New insights in the follow-up of differentiated thyroid carcinoma

Persoon, Adrienne Cornelia Maria

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Adrienne C. M. Persoon

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STELLINGEN

behorende bij het proefschrift

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Adrienne Persoon

4 maart 2009

1. Nu door het gebruik van ultrasensitieve thyreoglobuline (Tg) bepalingen bij veel patiënten lage maar nog juist aantoonbare concentraties worden aangetoond, moeten nieuwe 'evidence-based' Tg afkapwaardes voor aanvullend onderzoek worden vastgesteld om overbodige diagnostiek bij deze patiënten te voorkomen. *(dit proefschrift)*
2. Landelijke harmonisatie van thyreoglobuline bepalingen is broodnodig om resultaten van diagnostiek en behandeling beter te kunnen vergelijken. *(dit proefschrift)*
3. De recovery methode is een elegante wijze om in sera met thyreoglobuline antistoffen te bepalen of er daadwerkelijk sprake is van interferentie in de Tg meting en verdient hernieuwde aandacht. *(dit proefschrift)*
4. De beperkte diagnostische opbrengt, de hoge kosten en de negatieve invloed op kwaliteit van leven maken dat er geen plaats is voor routinematig gebruik van de door recombinant humaan TSH gestimuleerde Tg meting in de lange termijn follow-up van patiënten met gedifferentieerd schildkliercarcinoom. *(dit proefschrift)*
5. Zorgen over schildklierkanker persisteren bij patiënten met een aantoonbaar recombinant humaan TSH gestimuleerd Tg, ondanks dat er bij aanvullend onderzoek geen aanwijzingen zijn gevonden voor een recidief. *(dit proefschrift)*
6. Embolisatietherapie bij botmetastasen van gedifferentieerd schildkliercarcinoom vermindert pijn en neurologische symptomen. *(dit proefschrift)*
7. Patiënten die ziektevrij zijn na behandeling voor gedifferentieerd schildkliercarcinoom hebben een normale residuele levensverwachting, echter de mediane levensverwachting van patiënten met persisterende ziekte is gereduceerd tot 60%.
   (T.P. Links et al, Endocrine-related cancer 2005;12:273-280)
8. Met een beter inzicht in de resultaten van nacontrole in de oncologie wordt valse hoop voorkomen en onnodige medicalisering tegengegaan. *(Gezondheidsraad. Nacontrole in de oncologie. Doelen onderscheiden, inhoud onderbouwen. Den Haag: Gezondheidsraad, 2007)*
9. Zorg is een kwestie van mentaliteit en beschaving. Niet de marktwerking maar solidariteit dient het leidend beginsel in de zorg te zijn. *(bisschop Muskens)*
10. Voor het beheersen van de geneeskunst moet je eerst de kunst kunnen afkijken, de meester-gezelrelatie moet daarom de basis blijven van de opleiding tot medisch specialist.
11. Landbouwgrond omzetten in natuurgebied is een contradictio in terminis.

Persoon, A.C.M.
New insights in the follow-up of differentiated thyroid carcinoma.
Proefschrift Groningen. Met literatuur opgave. Met samenvatting in het Nederlands.

ISBN: 978-90-367-3713-5

The research presented in this thesis is supported by an effectiveness grant from the University Medical Center Groningen. Additional financial support by the following sponsors for the publication of this thesis is gratefully acknowledged:
AstraZeneca, Bayer, Brahms, Graduate School for Drug Exploration (Guide), Groninger Endocrinologie Stichting (Grendos), Martini ziekenhuis Groningen, Novartis Pharma BV, Pfizer, Rijksuniversiteit Groningen, Stichting Edu Cardio Groningen.

Typesetting and lay-out: Gildeprint Drukkerijen – Enschede
Printed by: Gildeprint Drukkerijen – Enschede

CMG.

rijksuniversiteit groningen

New insights in the follow-up of differentiated thyroid carcinoma

Proefschrift

ter verkrijging van het doctoraat in de
Medische Wetenschappen
aan de Rijksuniversiteit Groningen
op gezag van de
Rector Magnificus, dr. F. Zwarts,
in het openbaar te verdedigen op
woensdag 4 maart 2009
om 16.15 uur

door

Adrienne Cornelia Maria Persoon

geboren op 28 maart 1978

te Uithuizen

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Zing, vecht, huil, bid, lach, werk en bewonder
Ramses Shaffy

Contents

Chapter 1

Introduction and aim of the thesis

Introduction

Differentiated thyroid cancer (DTC) develops from thyroid follicular cells. It is the most common form of thyroid cancer, accounting for about 90% of all cases, and includes both papillary and follicular thyroid carcinomas (including Hürthle cell) (1). DTC is an uncommon tumor, as it affects approximately 24,826 individuals annually in Europe. It is 2-4 times more frequent in females than in males (2,3). Although it is a rare disease, the incidence of thyroid cancer has increased faster than that of any other malignancy in recent years (4). This is mainly due to the increased use of medical technology, including neck ultrasound and fine needle aspiration cytology. The known high prevalence of clinically occult tumors at autopsy (5,6) indeed suggests that increased diagnostic scrutiny has caused an apparent increase in incidence of cancer rather than a real increase (7). The overall prognosis of thyroid cancer is favorable with reported 10-years survival rates of 80-95% (8,9).

Initial treatment of differentiated thyroid cancer consists of total thyroidectomy (with lymph node dissection when indicated) and ablation therapy with radioactive iodine (I-131). Patients with residual and/or metastatic disease are usually treated by cyclic treatments with I-131 until complete remission is reached. Suppressive therapy with thyroid hormone is then initiated in order to prevent symptomatic hypothyroidism and to diminish the risk of recurrent disease. Growth of follicular cell-derived cancers cells depends on TSH: suppression of endogenous TSH is thought to deprive these cells of an important growth-promoting influence.

After a remission has been reached long-term follow-up is initiated. The primary objective in the follow-up is to detect and localize recurrent disease as early as possible. Recurrence of DTC occurs in up to 20% of patients (8,9,10). Most recurrences are detected during the early years of follow-up, but may be found even after several decades (11). Therefore lifelong follow-up of DTC patients is required. Traditionally, the cornerstone of follow-up is the measurement of serum thyroglobulin (Tg). Tg is produced only by thyroid follicular cells and provides the physical backbone for thyroid hormone synthesis (12). The tissue-specific origin of Tg biosynthesis has led to its widespread use as a tumor marker for DTC. To measure Tg, optimal biochemical assays with high precision and accuracy are essential. The detection limit of Tg assays is critical for the early detection of small amounts of Tg and to follow a change in Tg concentration. Recently, increasingly sensitive Tg assays have become available, but their actual clinical benefit needs to be ascertained.

The diagnostic accuracy of Tg measurement is hampered by interference from Tg antibodies (TgAb). TgAb may cause falsely high or low Tg values depending on the type of antibody and the type of Tg method used. Falsely low values may lead to late diagnosis of recurrence and a delay in necessary treatment. Alternatively, a falsely elevated Tg level can lead to an incorrect diagnosis of tumor recurrence, subsequent unnecessary scans or treatment and cause patient anxiety. Unfortunately, no currently available Tg method is guaranteed free of

TgAb interference (13). Detecting TgAb interference is technically challenging. Quantitative TgAb measurement, Tg recovery testing and intermethod comparison of Tg assays (radioimmunoassay / immunometric assay discordance) are available methods for assessing TgAb interference. But all these techniques suffer from shortcomings in technical performance or availability. Since approximately 25% of DTC patients have TgAb detected in their serum (13,14) further development of reliable methods for detecting TgAb interference is crucial.

Optimal sensitivity of Tg measurement can be reached when the measurement is performed after thyroid hormone withdrawal to elevate TSH level. This will cause a significant increase of Tg, which can then be more readily detected biochemically. Administration of recombinant human TSH (rhTSH) has proven to be an effective alternative to thyroid hormone withdrawal. It also stimulates the release of Tg by thyroid remnants and metastatic lesions of differentiated thyroid carcinoma, but does so without inducing the side effects of hypothyroidism due to thyroid hormone withdrawal, which are often poorly tolerated by patients (15,16). The rhTSH procedure consists of an intramuscular injection on day 1 and day 2, Tg levels are subsequently measured on day 5.

In the first year follow-up after initial therapy, most centers apply (rh)TSH stimulated Tg measurement, diagnostic I-131 whole body scan (WBS) and neck ultrasound to evaluate treatment response. When these methods show no abnormalities, patients are considered in complete remission. Although variation in methods during the first year is modest, the optimal management of DTC patients in the long-term follow-up phase (after reaching complete remission) is unclear. Uncertainty exists particularly about the appropriate method of Tg measurement. Some authors consider Tg measurement during thyroid hormone suppression therapy (Tg-on) sufficient for detection of recurrences in low-risk patients (17,18,19). Others favour periodic rhTSH stimulated Tg measurement (20,21), arguing that residual tumor may exist in patients with an undetectable Tg-on. Previous studies evaluating rhTSH stimulated Tg measurement in the follow-up of DTC included a heterogeneous group of patients in different phases of follow-up, and were often retrospective (22,23). Moreover, the potential contribution of the recently introduced highly sensitive Tg assays was not addressed. It is likely that these sensitive Tg assays increase the clinical utility of Tg-on measurement, reducing the need for measuring Tg after the expensive injection of rhTSH. However, we lack a prospective study during long-term follow-up in which the diagnostic yield of rhTSH stimulated Tg measurement is compared with Tg-on measurement with a sensitive Tg assay. Additionally, the influence of rhTSH stimulated Tg measurement (and the possible subsequent diagnostic tests) on quality of life has never been studied. Moreover, the rhTSH procedure and eventual subsequent diagnostic tests are expensive and the cost-effectiveness still has to be established.

Although the majority of patients with DTC have an excellent prognosis, patients with distant metastases (7% at initial diagnosis) are known to have a markedly reduced survival rate of 34% at 10 years (24). About 3 to 5% of patients with DTC develop bone metastases

(24,25,26). Bone metastases are less frequent than pulmonary metastases but carry a far worse prognosis (24,26). When bone metastasis have been demonstrated, both improvement of survival and palliation are the treatment goals. Therapeutic options include radioiodine therapy, surgical removal, external radiotherapy and possibly treatment with radio-labeled octreotide. Additionally, in 1980 selective embolization therapy (SET) for bone metastasis of DTC has been described for the first time (27). A few studies have been published, showing a rapid relief of pain and neurological symptoms after SET (28,29). Since the available data on SET concern small study populations, ongoing evaluation of this treatment modality, including its effect on survival, is needed.

Aim of the thesis

In this thesis we evaluate the follow-up and treatment of patients with differentiated thyroid carcinoma. We investigated the clinical utility of monitoring methods used in the long-term follow-up of patients with differentiated thyroid carcinoma, with the emphasis on different aspects of serum thyroglobulin measurement. Additionally, we evaluated the effect of a specific treatment modality, selective embolization therapy, for patients with bone metastases from differentiated thyroid carcinoma. The specific aims of this thesis are:

1. *Thyroglobulin (Tg) and thyroglobulin antibodies (TgAb)*
    a. To investigate the analytical and clinical performance of a new automated immunochemiluminometric assay for Tg in patients in follow-up for differentiated thyroid carcinoma (chapter 2).
    b. To assess the clinical utility of recovery testing in detecting interference in serum Tg measurement in patients with differentiated thyroid carcinoma (chapter 3). The Tg Recovery assay is compared with quantitative TgAb testing and the methodological benchmark for TgAb interference, radioimmunoassay / immunometric assay discordance, in relation to the clinical status of the patient.

2. *Recombinant human TSH (rhTSH) stimulated thyroglobulin measurement*
    a. To investigate the diagnostic yield of a sensitive Tg assay and rhTSH stimulated Tg measurement in the detection of a possible recurrence in the long-term follow-up of differentiated thyroid carcinoma (chapter 4).
    b. To investigate quality of life, and the impact of the use of rhTSH stimulated Tg measurement and eventual subsequent diagnostic tests on quality of life, in patients in long-term follow-up for differentiated thyroid carcinoma (chapter 5).

c. To investigate the cost-effectiveness of rhTSH stimulated Tg measurement in the long-term follow-up of differentiated thyroid carcinoma (chapter 6) These three aims were addressed in a prospective study in patients who were in long-term follow-up for differentiated thyroid carcinoma, and who on clinical grounds were considered to be disease-free.

3. *Embolization of bone metastases*
   a. To assess the effect of selective embolization therapy on symptoms and serum thyroglobulin in patients with bone metastases from differentiated thyroid carcinoma. Additionally, we investigated if selective embolization therapy has influence on life expectancy. This was evaluated in a retrospective study (chapter 7).

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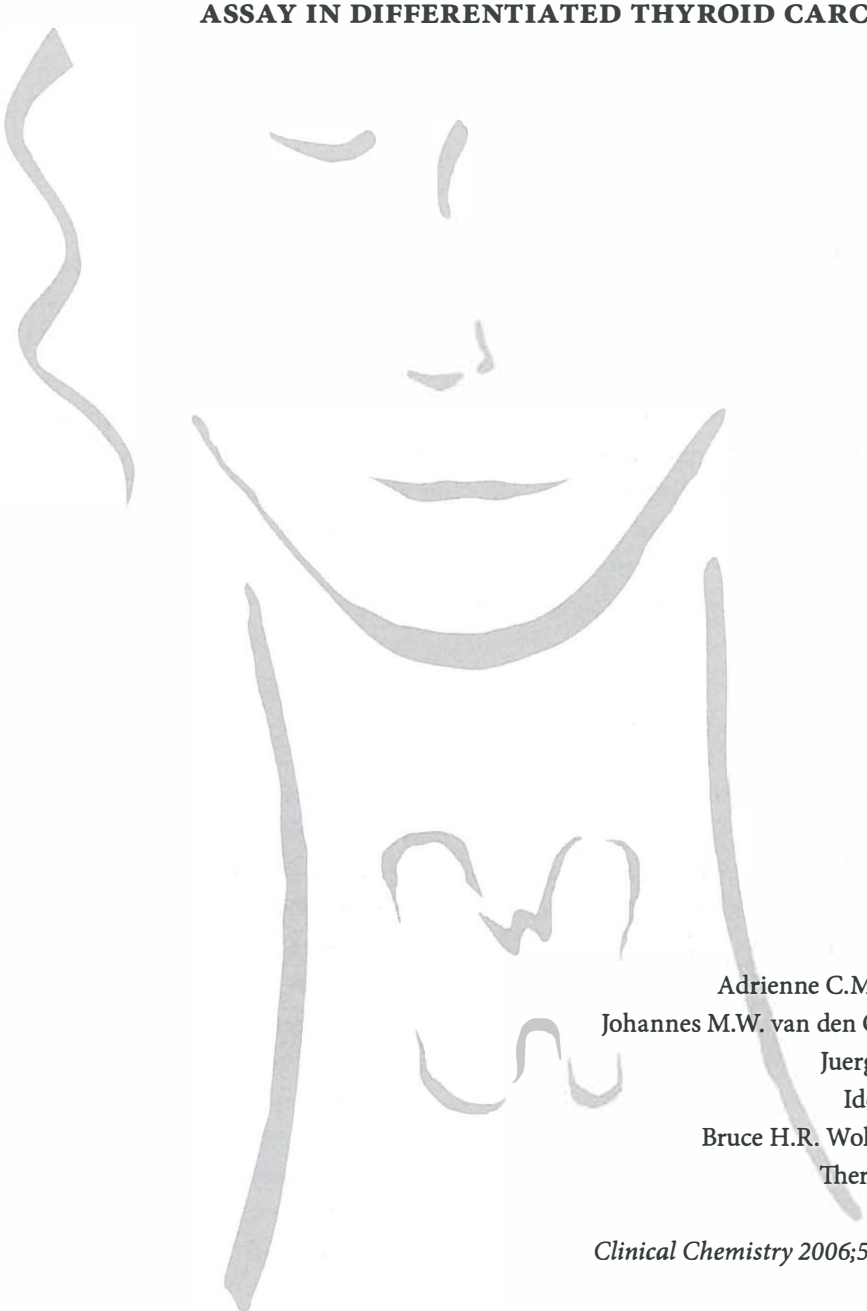
Chapter 2

Clinical utility of an automated immunochemiluminometric thyroglobulin assay in differentiated thyroid carcinoma



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Clinical Chemistry 2006;52:686-691

Abstract

Background: Thyroglobulin (Tg) measurements are important in the follow-up of patients with differentiated thyroid carcinoma (DTC). We evaluated the analytical and clinical performance of a new automated immunochemiluminometric assay for Tg (Tg-ICMA; Nichols Advantage Tg; Nichols Institute Diagnostics).
Methods: We used the Tg-ICMA to measure Tg concentration in serum samples from 110 Tg antibody-negative DTC patients undergoing thyroid-hormone suppression therapy. Disease state at the time of measurement was assessed on the basis of routine follow-up data. We compared the clinical performance of this assay with the routinely used immunoradiometric assay (Tg-IRMA, ELSA-hTG; CIS Bio International).
Results: The detection limit and functional sensitivity of the Tg-ICMA, based on direct calibration to CRM-457, were 0.05 and 0.6 µg /L, respectively. No Tg-IRMA-positive cases were missed by the Tg-ICMA. Tg was measurable by Tg-ICMA (0.6-8.6 µg/L) but undetectable by Tg-IRMA (< 1.5 µg/L) in 12 patients (11%). Clinical data showed evidence of disease in 4 of 12 patients (33%).
Conclusion: The Tg-ICMA is a sensitive and reproducible assay for identifying patients in follow-up for DTC with evidence of disease, but uncertainty remains with regard to interpreting findings of measurable serum Tg in patients with no evidence of disease. Follow-up data are required to determine the predictive value of these isolated Tg results. New concepts, i.e., serial Tg measurements and risk stratification of patients, need to be tested to confirm the applicability of this assay for clinical practice.

Introduction

High-quality thyroglobulin (Tg) assays are needed because of the fundamental role of Tg measurements in the postoperative monitoring of patients with differentiated thyroid carcinoma (DTC). Tg is a very large and heterogeneous glycoprotein that serves as the prohormone for thyroid hormone synthesis. Tg is used as a tumor marker because thyroid cells are the only source of Tg in the human body (1). Thus, the presence of Tg after total thyroidectomy and ablative I-131 therapy indicates persistence or recurrence of DTC. In particular, increasing serum Tg concentrations are an early and reliable indicator of recurrent disease (2).

Several Tg assays have been developed, but these assays are prone to methodologic problems, such as differences in standardization, suboptimal assay sensitivity and interassay precision, hook effects and interference attributable to Tg antibodies (TgAb) (2). A lack of standardisation can lead to difficulties with intermethod comparison of Tg results. Tg methods can also be too insensitive for monitoring DTC patients for disease recurrence. Poor interassay precision can make it impossible to reliably detect small changes in tumor size.

Furthermore, the hook effect in sera with very high Tg concentrations can lead to falsely low Tg values. Interference by TgAb leads to over- or underestimation of Tg concentrations, depending on the method used (2,3). No current Tg method is devoid of TgAb interference in every patient (4).

Recently, fully automated chemiluminescence assays for Tg have been developed that use monoclonal antibodies specific for human Tg. These assays combine high sensitivity with short turnaround times (5,6). We evaluated the analytical and clinical performance of a new automated immunochemiluminometric assay for Tg (Tg-ICMA).

Material and Methods

Patients

Since 1978, the Department of Endocrinology of the University Medical Centre Groningen has treated and followed about 600 patients with DTC. The present study included all 131 consecutive patients who visited our outpatient clinic for follow-up during the period of May to September 2003.

All patients (mean (SD) age, 54 (17) years; 22% male; median follow-up 8 years (interquartile range, 2-18 years) see Table 1) previously underwent treatment with total thyroidectomy and lymph node dissection, if indicated, followed by I-131 treatment for ablation and, if necessary, for treatment of persistent or recurrent disease, when I-131 uptake persisted (as earlier described by Haveman et al. (7)). Initial tumor staging was performed according to the postoperative tumor node metastasis (TNM) classification (8).

At follow-up visits, patients underwent neck palpation and serum Tg and TgAb measurements during thyroid hormone suppression therapy, and further imaging, such as ultrasound or magnetic resonance imaging of the neck and mediastinum, when there was clinical suspicion of disease recurrence.

All patients received thyroid hormone suppression therapy at the time of sampling. Samples from small group op patients were assayed during initial treatment phase, after radioiodine ablation therapy or subsequent radioiodine therapy.

Tg and TgAb concentrations were measured with standard and additional methods as described below. Patients positive for TgAb (n= 17), as measured in one or both quantitative TgAb assays, were excluded because of possible interference in the Tg assay. Four patients had to be excluded because of incomplete laboratory test results. Serum results from the remaining 110 patients were used for further analysis.

Disease state at the time of measurement was assessed on the basis of routine follow-up data. "No evidence of disease" was defined as absence for at least 1 year of clinically detectable disease and of Tg detection by the routinely used Tg-IRMA during thyroid hormone treatment. In case of Tg measurement within 1 year after radioiodine therapy, no evidence

of disease was defined as a negative diagnostic or posttherapy I-131 whole-body scan or undetectable Tg after discontinuation of thyroid hormone treatment. Patient characteristics are shown in Table 1.

Table 1. Clinical characteristics of studied patients

Clinical characteristics	All patients[a] (n=131)	Patients included for analysis[b] (n=110)	Patients with discordant Tg results[c] (n=12)
Male –no.	29	22	5
Female –no.	102	88	7
Mean (SD) age –years	54 (17)	55 (17)	45 (15)
Histology –no.			
Papillary	85	71	10
Follicular	39	32	1
Hürthle cell	7	7	1
TNM[d] –no.			
T0	3	1	1
T1-T3	94	78	9
T4	20	18	2
Tx	14	13	0
N0	84	69	5
N1	42	34	7
Nx	7	7	12
M0	118	97	0
M1	12	12	0
Mx	1	1	
Age at initial diagnosis[e] -years	40 (32-54)	41 (32-54)	37 (25-47)
Follow-up[e] –years	8(2-18)	6(2-19)	6 (2-13)
Disease free period[e] –years	8 (2-18)	9(2-19)	7 (3-13)
Disease state at time of Tg measurement –no.			
No evidence of disease	95	81	8
Evidence of disease	36	29	4

[a] All patients enrolled at the start of the study.
[b] TgAb negative patients with complete laboratory results.
[c] Patients with detectable Tg in the ICMA and undetectable Tg in the IRMA.
[d] Postoperative TNM-classification (8).
[e] Median (interquartile range).

Tg assays

The established ELSA-hTG (CIS Bio International) Tg-IRMA is a solid-phase 2-site IRMA that uses two monoclonal antibodies, one coated on a solid phase and one labeled with I-125 and used as a tracer. Functional sensitivity (defined as the lowest concentration with an inter-assay CV ≤ 20%), was 1.5 μg/L. Inter-assay imprecision was 8% and 6.9% at 5 and 223 μg/L, respectively. The Tg-IRMA was not calibrated against the CRM-457 reference preparation.

The Nichols Advantage® Tg-ICMA (Nichols Institute Diagnostics) is a fully automated 2-step chemiluminometric sandwich immunoassay that uses 3 monoclonal antibodies: 2 are biotinylated and used for capture, and the third antibody is labeled with acridinium ester for emitted-light quantification. Throughput is up to 80 samples/h with a time to first result of 51 minutes. The Tg-ICMA was calibrated against the CRM-457 reference preparation. The limit of detection was determined by reading the +3 SD response from 10 replicate measurements of the zero calibrator from the stored master curve on 2 different occasions. We determined functional sensitivity (defined as the lowest serum Tg concentration for which the interassay imprecision (CV) did not exceed 20%) and between-run reproducibility by measuring human DTC serum pools with Tg concentrations of 0.66, 16 and 146 μg/L in 35 runs over a 7-month period with calibration on a weekly basis using 2 different lots of reagents. We tested interference by heterophilic antibodies (HAMAs) by remeasuring Tg after incubating 500 μL of serum sample in heterophilic blocking tubes (HBTs: Scantibodies) at room temperature for 1 h.

We used a third Tg assay for method comparison in a limited number of patient sera samples. This radioimmunoassay (Tg-RIA), with a functional sensitivity of 1 μg/L, was reported to have minimal interference from TgAb (4) and was developed by the University of Southern California Endocrine Services Laboratory (Los Angeles, CA).

Thyroglobulin antibody assays

Two different quantitative assays were used for TgAb detection. The Nichols Advantage TgAb assay (Nichols Institute Diagnostics) with a cut-off value for TgAb positivity of 2 mIU/L, and the AxSYM TgAb assay (Abbott Laboratories) with a cut-off value for TgAb positivity of 45 mIU/L. Both TgAb assays are referenced to the WHO TgAb First International Reference Preparation (WHO 65/93).

Thyrotropin assay

Serum thyrotropin (TSH) concentrations were measured by a time-resolved immunofluorometric assay on the DELFIA system (PerkinElmer Life Sciences).

Results

Analytical performance of the Tg-ICMA

The detection limit of the Tg-ICMA assay was 0.05 µg/L. For human DTC serum pools, Tg-ICMA inter-assay imprecision over a 7-month period was 19% at 0.66 µg/L, 5.5% at 16 µg/L and 12% at 146 µg/L. The functional sensitivity, defined as the lowest concentration of serum Tg for which the interassay CV did not exceed 20%, was set at 0.6 µg/L, based on the CV of 19% for the mean concentration of the low serum pool (0.66 µg/L).

We used Passing and Bablok regression analysis to compare DTC sera with measurable Tg in both the Tg-ICMA and Tg-IRMA, as shown in Figure 1. The regression analysis yielded the following equation: Tg-ICMA=1.87 (95% confidence interval, 1.69-1.96) x Tg-IRMA +3.01 (1.00-5.19); r = 0.992 (n=40). A limited number of TgAb-negative sera (n=8) with Tg concentrations ranging of 2-70 µg/L according to the Tg-ICMA assay were also tested by Tg-RIA; Passing and Bablok regression yielded the following equation: Tg-ICMA = 1.78 (1.71-1.87) x Tg-RIA +0.72 (0.16-1.240); r = 0,999). The Tg-RIA has been standardized against the CRM-457 reference preparation. A marked difference in results for the Tg-ICMA and Tg-IRMA/Tg-RIA methods was likely related to differences in monoclonal epitope specificity.

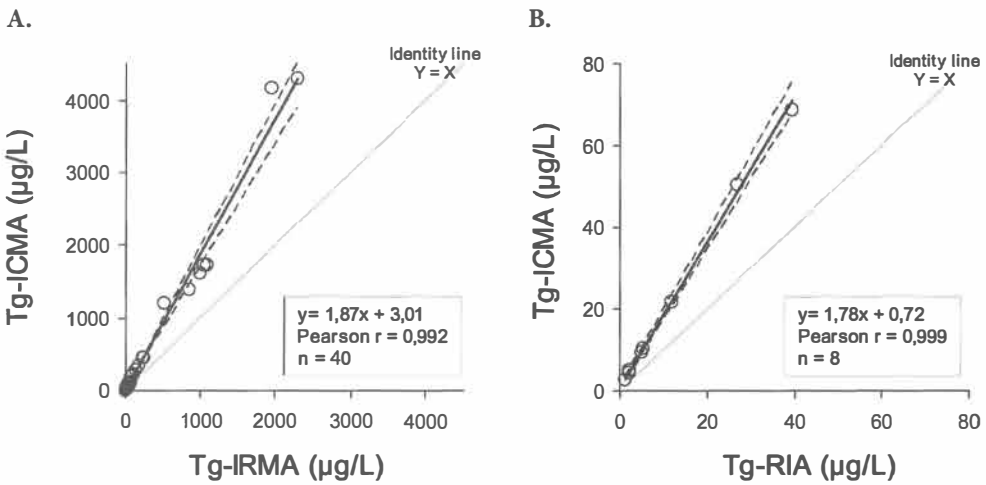

Figure 1. *Passing & Bablok regression analysis comparing the established Tg-IRMA (A) and Tg-RIA (B) with the Tg-ICMA.*

Comparison of results obtained with the different Tg methods for TgAb-negative sera. A total of 40 serum samples from 22 patients with measurable Tg in both the Tg-ICMA and Tg-IRMA were used. (A), serum Tg concentrations measured by Tg-IRMA and Tg-ICMA (n=40). (B), serum Tg concentrations measured by Tg-RIA and Tg-ICMA (n=8). The dashed lines represent 95% confidence intervals. The gray line indicates lines of unity.

Clinical performance of the Tg-IRMA and Tg-ICMA

We compared results obtained with both Tg assays and divided them into concordant and discordant results. Concordant results were Tg concentrations detectable in both assays (Tg-IRMA ≥ 1.5 µg/L and Tg-ICMA ≥ 0.6 µg/L) or Tg concentrations undetectable in both assays (Tg-IRMA < 1.5 µg/L and Tg-ICMA < 0.6 µg/L). Results were considered discordant when Tg concentrations were detectable in one assay and undetectable in the other assay. Disease state and Tg results were correlated (Table 2).

Table 2. Results of Tg assays divided into concordant and discordant results, related with disease state at time of measurement.

Tg assay results	No evidence of disease (n=77)	Evidence of disease (n=33)	Total[a] (n=110)
Concordant results			
Tg undetectable by IRMA and ICMA	69	7	76
Tg detectable by IRMA and ICMA	0	22	22
Discordant results			
Tg detectable only by ICMA	8	4	12

[a] TgAb-negative patients with complete laboratory results.

Concordant Tg results

Concordant results from both Tg assays were obtained for 98 patients. In 76 sera, no Tg was measurable by either the Tg-IRMA (< 1.5 µg/L) or the Tg-ICMA (< 0.6 µg/L), and in 22 sera Tg was measurable by both Tg assays, with Tg concentrations of 3.3-136000 µg/L in the Tg-IRMA and 9.2 to > 125000 µg/L in the Tg-ICMA.

Clinical data showed that of 76 patients with undetectable Tg results for both assays, 69 had no evidence of disease whereas 7 had evidence of disease at the time of measurement, and all 22 patients with detectable Tg results in both Tg assays had evidence of disease at the time of measurement.

Discordant Tg results

Discordant results were obtained in 12 patients (11%). In all of these patients, Tg was measurable by the Tg-ICMA (≥ 0.6 µg/L) but not by the Tg-IRMA (< 1.5 µg/L). The median (SD) Tg results obtained with the Tg-ICMA were 1.9 (2.2) µg/L (range 0.65-8.6 µg/L). The clinical characteristics of the 12 patients with discordant Tg results are shown in Table 1. Eight of these 12 patients had no clinical evidence of disease, whereas 4 (33%), with Tg concentrations ranging from 1.5 to 4.7 µg/L, had clinical evidence of disease, based on nuclear or radiologic imaging, at the time of measurement. The clinical characteristics and disease states of these 4 patients are shown in Table 3. As shown in Table 3, 1 of these 4 patients was assessed as having "clinical evidence of disease" during the initial treatment phase.

In 1 case we observed a marked discrepancy in serum Tg concentration measured by both Tg methods: serum Tg was 8.6 μg/L by the Tg-ICMA and < 1.5 μg/L by the Tg-IRMA. Because Tg was not detected (< 1.0 μg/L) by the Tg-RIA, we incubated the serum in HBTs to determine whether the increased Tg result for the Tg-ICMA assay was attributable to interference from heterophilic antibodies. The Tg concentration decreased to 1.2 μg/L after incubation in HBTs, indicating interference by heterophilic antibodies.

Table 3. Clinical data of patients with detectable Tg only by ICMA assay and clinical evidence of disease.

Patient	Age/Sex[a]	Histology	TNM[b]	Follow-up (years)	Tg-ICMA μg/L	Tg-IRMA μg/L	Disease state[c]
1.	39/F	Pap[d]	T4N1M0	4	1.5	<1.5	Persistent disease; detectable Tg (IRMA) during withdrawal; negative last posttherapy scan; suspicious pre-/paratracheal neck foci on MRI
2.	55/M	Fol	T0N1M0	8	4.67	<1.5	Repeatedly marginally detectable Tg concentrations (IRMA) previous years; no identifiable disease remnant
3.	33/F	Pap	T2 N1M0	0	2.8	<1.5	Initial treatment phase; abnormal neck uptake on postablation WBS.
4.	41/M	Pap	T2 N1M0	1	2.7	<1.5	Persistent disease; suspicious paratracheal mass on MRI

[a] Age in years.
[b] Postoperative TNM classification (8).
[c] Disease state at time of Tg measurement.
[d] Pap, papillary; Fol, follicular; MRI, magnetic resonance imaging; WBS, whole-body scan.

Discussion

In this study the analytical performance of the new ICMA was characterized by high sensitivity with a detection limit of 0.05 μg/L and a functional sensitivity of 0.6 μg/L. Additional benefits of this ICMA were its full automation, nonradioactive design, high reproducibility, and short time to result. Clinical performance showed that for 12 of the 110 DTC patients (11%), 4 (33%) of whom had clinical evidence of disease at the time of measurement, Tg was detected by ICMA but not by IRMA.

In the postoperative follow-up of DTC patients, the main objective is the identification of patients who have residual tumour or develop a recurrence. Serum Tg detection in the follow-up phase indicates the presence of residual healthy thyroid tissue or metastatic disease (9). Thus, important clinical decisions such as whether patients should undergo diagnostic or therapeutic procedures are based on the measurement of the serum Tg concentration in

individual patients (10), as is supported by the prominent place of the assay for (recombinant) TSH-stimulated Tg concentration in follow-up protocols (11,12).

The sensitivity of Tg measurements can be optimized by clinical and technical improvements (13). Clinically, measurements of TSH stimulated Tg after thyroid hormone withdrawal or exogenous TSH administration in patients with undetectable serum Tg during thyroid hormone suppression therapy is currently recommended for unmasking occult disease (12,14). Technically, the development of Tg assays with improved functional sensitivity enhances the value of Tg measurements. The Tg-ICMA meets the criterion proposed by an expert panel (11,12) that a Tg assay should have a functional sensitivity of at least 1 μg/L.

Standardization or specificity differences can lead to between-method biases. The Tg-ICMA and Tg-RIA are both standardized to CRM-457, whereas the Tg-IRMA is not. Tg-IRMA results are approximately 20% lower when the Tg-IRMA standardization is compared with CRM-457 (manufacturer's information). The approximately 2- to 3-fold higher readings obtained with the Tg-ICMA compared with both Tg-IRMA and Tg-RIA more likely reflect differences in the number and epitope specificities of the Tg monoclonal antibody reagents used by the manufacturers and differences between the nonserum calibrator matrices and patient sera (15). Accordingly, Spencer et al. (16) recently showed wide biases among 10 tested immunometric methods and attributed this finding to differences in assay specificities for circulating Tg isoforms rather than differences in assay standardization. Despite the 2- to 3-fold higher reading obtained with the Tg-ICMA, it has a far lower detection limit (0.6 μg/L) than the Tg-IRMA (1.5 μg/L); thus, 4 additional patients with evidence of disease were identified by the Tg-ICMA but not the Tg-IRMA.

The significance of the low Tg concentrations detectable by Tg-ICMA in the remaining 8 patients in this study is unclear. Because detectable serum Tg in the follow-up phase has always been associated with the presence of residual healthy thyroid tissue or metastatic disease (9,17), these data could identify a population at high(er) risk for recurrence. Such findings could enable risk stratification on the basis of Tg result and patient characteristics and the development of follow-up protocols more adapted to individual patients. On the other hand, lower specificity for the presence of recurrent thyroid cancer is a possible limitation of more sensitive Tg assays. Most of the 8 patients with Tg detectable by ICMA but no by IRMA and with no evidence of disease had undergone follow-up for years and had a mean disease-free period of 8 years. The present study had a cross-sectional design, and clinical evaluation was based on clinical history. Previous follow-up studies have shown that not all patients with detectable Tg will develop recurrent disease (18,19). Zöphel et al. (20) observed that in 96% of DTC patients in remission with initial low Tg concentrations (0.03-0.8 μg/L by Tg ELISA), Tg concentrations were essentially unchanged during a 4-year observation period, and all of these group remained well. Of the 5 patients (4%) in whom Tg concentrations increased, all but 1 had recurrence of DTC.

Interpretation of the low detectable Tg values obtained in our study is uncertain, but such findings may give rise to possibly unnecessary concern and even excessive diagnostics. Therefore, follow-up data of this Tg assay are required to interpret the finding of isolated Tg values and justify the performance of additional diagnostics in this group of patients. Moreover, because a change in serial Tg measurement during follow-up may be more informative for recurrence of disease than an absolute value of Tg in the lower range, prospective data for these patients could provide valuable information (20).

Although sensitivity is optimized in this assay, 7 patients with evidence of disease had Tg concentrations below the functional sensitivity of the ICMA, suggesting that the sensitivity is suboptimal for managing patients with DTC (21). Moreover, Spencer et al. (16) recently showed that interference in Tg measurement by TgAb cannot be excluded when TgAb are not detectable. Tg was reported undetectable in euthyroid control subjects without evidence of TgAb. Consequently, "confidence in the specificity of a negative antibody report with an undetectable serum Tg becomes less secure" (21). Furthermore, TgAb assays vary considerably in sensitivity and specificity, probably because of differences in assay specificities for the conformational epitopes characteristic of endogenous TgAb (16). Therefore, in our study, the 7 patients with evidence of disease but undetectable Tg by ICMA may have serum TgAb that cannot be detected by the methods used. Similarly, Spencer et al. (16) reported poor concordance of TgAb detection among 12 direct TgAb methods. In addition, tumor dedifferentiation can lead to an abscense of Tg synthesis or synthesis of Tg with altered biochemical features, obscuring recognition by the antibodies used in the Tg assay (22). Therefore, low or even undetectable Tg does not guarantee absence of recurrent or metastatic disease (22,23).

Immunometric methods can also be subject to interference from heterophil antibodies (HAMAs), leading to inappropriately high serum Tg values (5,6). Recently, Preissner et al.(5) showed that HAMA interference is relatively prevalent (1.5%-3%) in a commonly used automated Tg assay and can lead to clinically significant artifacts. The Tg-ICMA assay appears to suffer from similar problems, as shown in the case reported here, despite the fact that the manufacturer has added mouse serum in the assay procedure as a precautionary measure. The possibility that HAMA interference played a role in the other discrepant cases in our study cannot be ruled out but is unlikely because the discrepancies in these cases can be explained by the difference in absolute readings between the Tg assays. However, interference from HAMAs should be considered if the Tg result does not fit the clinical picture. Further investigation, by repeated testing with a different Tg assay, testing serial dilutions or treatment with additional blocking reagents, is advocated.

In conclusion, the new ICMA is a robust and sensitive Tg assay that optimizes the identification of patients with disease activity during follow-up of DTC. Because Tg is detectable by the ICMA in some patients with no clinical evidence of disease, follow-up data of these patients are needed to demonstrate the applicability of this Tg assay in clinical practice.

Acknowledgements

We thank J. Koerts and E. Heine for technical assistance and Nichols Institute Diagnostics for support. We thank Dr. C.A. Spencer for the performed Tg measurements with the Tg-RIA assay.

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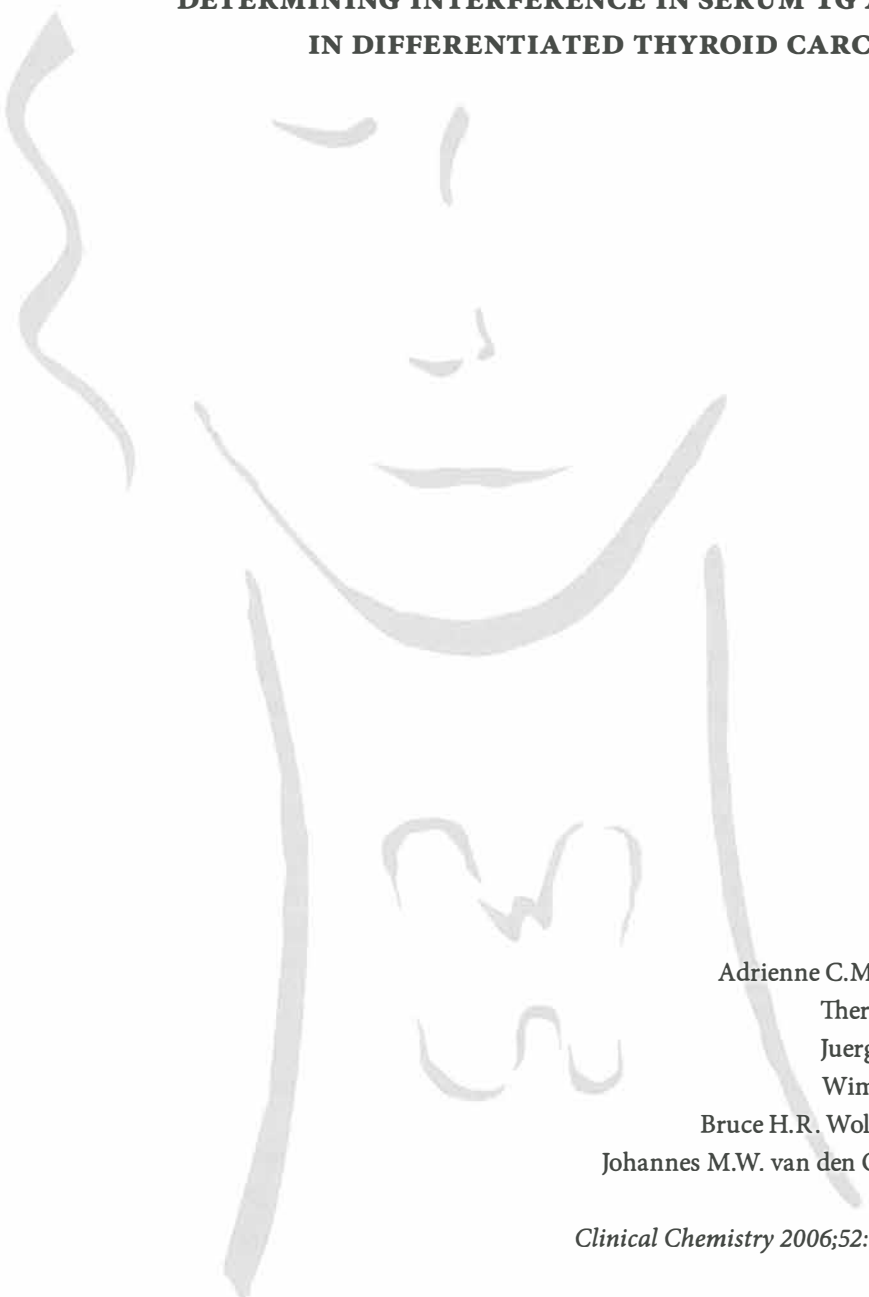
Chapter 3

Thyroglobulin (Tg) recovery testing with quantitative Tg antibody measurement for determining interference in serum Tg assays in differentiated thyroid carcinoma



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Clinical Chemistry 2006;52:1196-1199

Abstract

Background: Thyroglobulin (Tg) measurements are complicated by interference from Tg antibodies (TgAbs) or heterophilic antibodies (HAMAs). We used a new automated immunochemiluminometric assay (ICMA) with Tg recovery (TgR) on the Nichols Advantage® platform to reassess the clinical utility of recovery testing in detecting interference in serum Tg measurement in patients with differentiated thyroid carcinoma.
Methods: We used 2 TgAb methods to detect Tg measurement interference with TgR and quantitative TgAb measurement in sera from 127 patients. In a limited number of samples, we used a radioimmunoassay (Tg-RIA) as comparison method because it appeared to be minimally affected by TgAb.
Results: Prevalence of TgAbs was 13% (17 of 127) in either 1 or both TgAb assays. A compromised TgR (< 70%) corresponded with TgAb positivity in either TgAb assay for 10 of 11 samples (91%), whereas a normal TgR (≥ 70%) corresponded with TgAb negativity in both assays for 95 of 101 samples (94%). In 6 TgAb-positive sera with TgR within the reference interval, there were no discrepancies between RIA and ICMA results. We obtained discordant RIA and ICMA results for 6 of 9 TgAb-positive sera with decreased TgR. In 1 TgAb-negative sample, the Tg result was falsely increased because of interference by HAMAs, as shown by an overrecovery of 126%.
Conclusions: The Nichols Advantage TgR assay is a valuable complementary method to overcome the technical problem of interference by TgAbs or HAMAs in TgAb assays. Further studies are needed to confirm the potential added value of this TgR assay.

Serum thyroglobulin (Tg) measurements play a key role in the postsurgical follow-up of patients with differentiated thyroid cancer (DTC) (1), but these measurements are severely hampered by the presence of Tg antibodies (TgAbs), which can cause under- or overestimation of Tg concentration depending on the Tg assay format (2,3). The National Academy of Clinical Biochemistry guideline (4) recommends the use of sensitive TgAb immunoassays to detect TgAbs in favor of Tg recovery (TgR) testing because TgR testing fails to differentiate TgAb-positive and -negative sera (5,6). The differences in immuno-reactivity between endogenous Tg and Tg added to patient serum, as well as the amount of Tg added and the duration of incubation, all appear critical to the TgR result (5,7). However, limitations of TgAb testing are also recognized: TgAb concentrations do not correlate with the degree of interference (3,8); TgAb positivity does not indicate interference per se; substances other than TgAbs can interfere with Tg measurement (9); and TgAb detection is strongly method dependent (10).

A reliable hallmark of TgAb interference is the presence of RIA/immunometric assay discordance (4,10), but intermethod comparisons are impractical because few RIAs are available (10). Therefore, the technical problem of TgAb interference in Tg measurements

has not been overcome. The release of a new TgR assay enabled us to reassess the clinical utility of recovery testing in detecting interference in serum Tg measurements by comparing the TgR assay with a quantitative TgAb test and the methodological benchmark for TgAb interference, RIA/immunometric assay discordance (10), in relation to the clinical status of the patient.

We collected sera from 127 patients with DTC undergoing thyroid hormone suppression therapy who visited our outpatient clinic between May and September 2003. No evidence of disease was defined as absence of clinical, scintigraphic, or radiologic evidence of recurrent or persistent disease, including undetectable Tg with an immunoradiometric assy (IRMA, ELSA-hTg, CIS bio international; functional sensitivity (defined as the lowest concentration for which the interassay CV did not exceed 20%), 1.5 µg/L) during thyroid hormone suppression therapy for at least 1 year (for the clinical characteristics of the patients, see Table 1).

Table 1. Clinical characteristics of the study patients

	All patients n=127	TgAb positive patients[a] n=17
Age –yrs[b]	57 (19-85)	61 (25-82)
Sex –no		
Female	104	16
Male	23	1
Histology –no		
Papillary	86	16
Follicular	33	
Hürthle	8	1
TNM stage[c] –no		
T0	1	
T1-T3	88	10
T4	23	5
Tx	15	2
N0	78	9
N1	42	8
Nx	7	
M0	111	14
M1	15	3
Mx	1	
Follow-up-yrs[b]	6 (0-43)	3 (0-29)
Disease state[d] -no		
No evidence of disease	95	14
Evidence of disease	32	3

Clinical characteristics of all patients and of the subgroup of TgAb-positive patients.
[a] TgAb positivity in TgAb-ICMA and/or TgAb-MEIA assay.
[b] Median (range).
[c] Postoperative TNM classification (14).
[d] Disease state at time of sampling.

We performed serum Tg measurements with a fully automated 2-step immunochemiluminometric assay (Tg-ICMA) that used 3 monoclonal antibodies (Advantage®, Nichols Institute Diagnostics). The assay characteristics are reported elsewhere (11).

In a limited number of samples, we used a Tg-RIA as the comparison method because it appeared minimally affected by TgAb (5,10).

Both the Tg-ICMA and Tg-RIA were calibrated against the CRM-457 reference preparation, but the Tg-ICMA showed a 1.8-fold higher Tg reading, likely reflecting differences in assay specificity for circulating Tg isoforms (11). Tg-ICMA/RIA discordance, as a methodologic benchmark for TgAb interference, was defined as being present when there was a difference between both Tg assays after correction for the 1.8-fold difference and each method's reproducibility (CV).

TgAb measurements were performed either by chemiluminescence immunoassay (TgAb-ICMA performed on an Advantage; Nichols Institute Diagnostics) or by microparticle enzyme immunoassay (TgAb-MEIA, performed on an AxSYM; Abbot Diagnostics). Interassay imprecision profiles, as determined by measuring human DTC serum pools with various TgAb concentrations in 20 runs over a 2-week period with 2 different lots of reagents, were 79%, 19%, and 13% at 0.1, 2 and 75 kilounits/L, respectively, for the TgAb-ICMA and 23%, 11% and 7% at 31, 155 and 522 kilounits/L, respectively, for the TgAb-MEIA. The cut-off values used for TgAb positivity, based on the lowest TgAb concentrations in serum for which the interassay CV did not exceed 20% (functional sensitivity), were 2 and 45 kilounits/L for the TgAb-ICMA and TgAb-MEIA, respectively. These values were slightly higher than the manufacturers' cut-off limits of 1 and 34 kilounits/L, respectively. Both TgAb assays are referenced to the WHO Tg autoantibodies First International Reference Preparation (WHO 65/93).

We performed TgR testing with a new recovery assay on the Nichols Advantage platform by adding 10 μg/L of purified human Tg in DTC sera with Tg-ICMA concentrations < 80 μg/L. We measured Tg in sera with (Tg2) and without (Tg1) added Tg (aTg) and calculated the percentage recovery from the formula: [(Tg2-Tg1)/aTg] x 100.

Tg, TgAb, and TgR results and clinical data for all TgAb-positive patients are summarized in Table 2.

The prevalence of TgAbs was 13% (17 of 127) in either one or both TgAb assays. TgAbs were detected in 12% (16 of 127) with the TgAb-ICMA and in 10% (13 of 127) with the TgAb-MEIA, and 9% (12 of 127) showed positivity in both assays. The intermethod variability for the detection of TgAbs likely resulted from differences in assay sensitivity and specificity despite standardization against WHO 65/93 (10). The prevalence of TgAbs in our DTC patients (10%-12%) seemed to be lower than the prevalences reported by others (20%-30%) (5,12). Nevertheless, our results correspond with previous data (9) reporting a TgAb prevalence in DTC patients of 29% at initial examination, decreasing to < 10% after 3 years follow-up. The median follow-up in our study was 4 years.

Table 2. Clinical data for TgAb-positive patients and assay results

TgAb measurable in both TgAb-ICMA and TgAb-MEIA[a]

Patient	Tg ICMA µg/L	Tg RIA µg/L	TgAb ICMA[b] kilounits/L	TgAb MEIA[c] (kilounits/L)	TgR %	Age (years) / Sex	Histology[d]	TNM[e]	Follow-up years	Disease state[f]
1	<0.6	<1	**4.4**	**46.9**	**68**	43/F	P	T2N1M0	1	NED
2	<0.6	**4.9**	**94.6**	**207.5**	**25**	73/F	P	T3N1M0	1	NED
3	<0.6	NA[g]	**18.6**	**48.6**	**63**	76/F	P	T2N1M0	27	NED
4	<0.6	<1	**20**	**74.8**	74	61/F	P	T3N0M0	2	NED
5	<0.6	<1	**17.6**	**49.5**	**56**	82/F	P	T4N0M0	3	NED
6	<0.6	**1.4**	**89.6**	**133**	**64**	49/M	P	TxN1M0	19	NED
7	<0.6	**1.0**	**119.9**	**140.6**	**62**	45/F	P	T4N1M0	4	NED
8	**4.5**	**2.1**	**2.1**	**91.7**	89	37/F	P	T2N0M1	0	ED
9	<0.6	**3.3**	**34.5**	**64.0**	**45**	41/F	P	T2N0M0	11	NED
10	<0.6	**6.5**	**760.4**	**>1000**	**40**	39/F	P	TxN1M1	29	NED
11	<0.6	<1	**44.3**	**125.4**	**62**	77/F	P	T4N0M0	3	NED
12	<0.6	**3.1**	**133.7**	**464.3**	**34**	76/F	P	T3N1M0	1	ED

TgAb only measurable in TgAb-ICMA[a]

13	<0.6	<1	5.1	**20.7**	85	27/F	P	T2N0M0	11	NED
14	<0.6	<1	5.7	**23.7**	82	25/F	P	T3N1M0	10	NED
15	<0.6	<1	3.4	**23.8**	95	67/F	P	T2N0M0	2	NED
16	**4167**	NA	2.3	**20.7**	ND[h]	70/F	H	T4N0M1	0	ED

TgAb only measurable in TgAb-MEIA[a]

17	<0.6	<1	<2.0	**49.1**	106	66/F	P	T4N0M0	27	NED

[a] Bold numbers indicate measurable serum Tg, TgAb positivity, or compromised Tg.
[b] Cut-off for positivity, 2 kilounits/L.
[c] Cut-off for positivity, 45 kilounits/L.
[d] Histology: P, papillary; H, hürthle cell
[e] TNM classification based on criteria listed in Ref. (14)
[f] Disease state at time of sampling, see text. NED, no evidence of disease; ED, evidence of disease.
[g] NA, not assessed.
[h] ND, recovery not determined because of high serum Tg concentration.

Evidence of disease was present in 3 of 17 (18%) TgAb-positive patients. Two patients (patient 12 and 16 in Table 2) had extensive metastatic disease. In the third patient (patient 8), TgAbs were measured shortly after radioiodine ablation therapy. Tg was detectable by Tg-ICMA in 2 of these 3 patients (Table 2).

We determined a reference interval for TgR by performing recovery testing in 96 TgAb-negative DTC sera. We obtained a nongaussian distribution ($P < 0.05$, Shapiro-Wilk nor-

mality test) with a slight left tail, with recoveries of 67%-125% (mean, 96%; 95% confidence interval, 70%-120%, see Figure 1A). TgR < 80% might reflect some form of interference, e.g. by autoantibodies not recognized by the TgAb assay or from substances other than TgAbs. To reveal possible interference, we used the Tg-RIA to retest samples from 5 of 7 patients with TgR values of 67.5% to 76.4% and a Tg-ICMA result < 0.6 µg/L. The Tg-ICMA and Tg-RIA results were concordant for 4 of 5 sera, providing no evidence for interference in Tg measurements. In 1 TgAb-negative patient with a slightly compromised recovery (67.5%), Tg-RIA/ICMA discordance (1.1 µg/L by Tg-RIA versus < 0.6 µg/L by Tg-ICMA) supported the recovery result, indicating serum Tg interference.

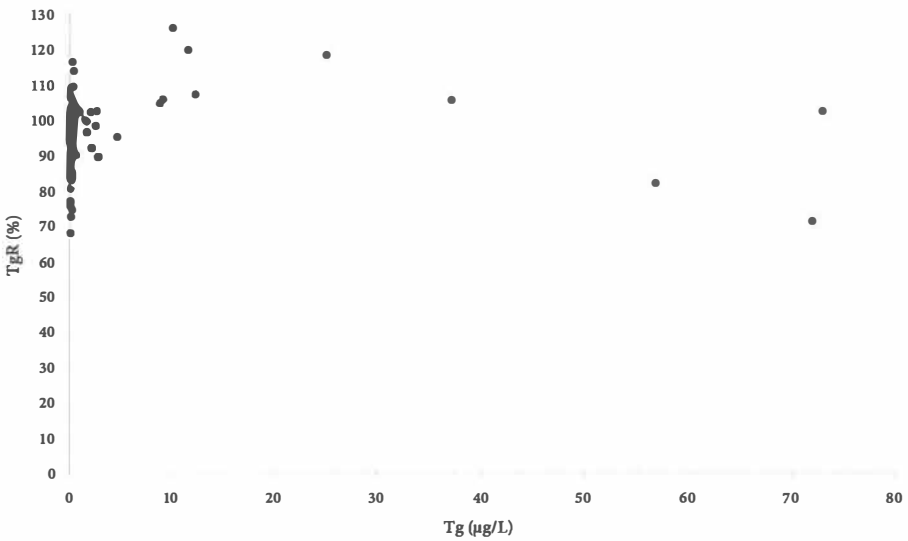

Figure 1A. *TgR in TgAb-negative sera.*

Percentage TgR in 96 TgAb-negative sera with Tg < 80 µg/L.

We suspected overrecovery in 1 sample with a TgR of 126%, a serum Tg-ICMA result of 8.6 µg/L, and Tg that was undetectable by RIA (< 1 µg/L) and by IRMA (< 1.5 µg/L; ELSA-hTg, CIS bio international). In this sample, the Tg-ICMA result was falsely increased as a result of interference by heterophilic antibodies (11). We therefore used 70%-120% as the reference interval for TgR.

TgR differed significantly in TgAb-negative (n=96) and TgAb-positive sera (n=17; P < 0.0005, Mann-Whitney U test). The TgR was compromised (< 70%) in 91% of samples (10 of 11) that tested positive for TgAbs in both TgAb assays, whereas the TgR was within the reference interval (≥ 70%) for 95% of samples that were negative for TgAbs in the TgAb-ICMA (96 of 101) and 97% of samples (98 of 101) that were negative in the TgAb-MEIA (Table 3).

Table 3. TgR, by Tg assay, in TgAb-positive and -negative patients.

	TgR < 70% n	TgR ≥ 70% n	Total n
ICMA			
Positive	10	5	15
Negative	1	96	97
Total	11	101	112
MEIA			
Positive	10	3	13
Negative	1	98	99
Total	11	101	112

Ten of 12 (83%) sera with positivity for TgAbs in both assays had compromised TgR. Considering the TgAb assays separately, 67% of the sera positive in the TgAb-ICMA (10 of 15) and 77% of the sera positive in the TgAb-MEIA (10 of 13) showed TgR < 70% (Table 3). Patients with higher TgAb titers showed more compromised recovery (Pearson correlation for TgAb-MEIA, r = 0.79 (P < 0.0003); for TgAb-ICMA, r = 0.55 (P < 0.03) (see Figure 1B and Figure 1C). Sera that were positive only in the TgAb-ICMA (n = 3) or the TgAb-MEIA (n = 1) had TgR within the reference interval (Table 2) and relatively low antibody titers.

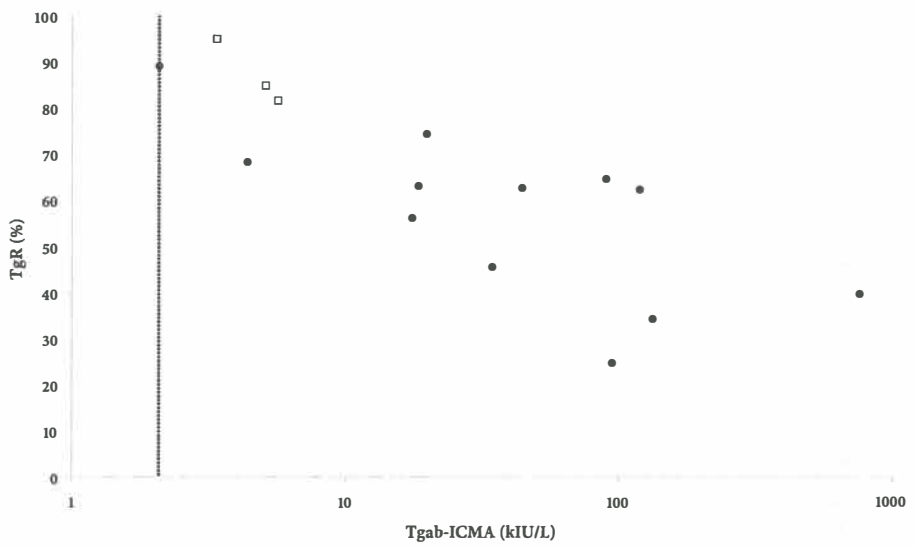

Figure 1B. *TgR in TgAb-ICMA positive sera.*

TgR in 16 TgAb-ICMA positive sera.
Cut-off value TgAb-ICMA positivity: 2 kilounits/L.
- *indicates sample with TgAb-positivity in both TgAb-ICMA and TgAb-MEIA.*
- □ *indicates sample with TgAb-positivity in only TgAb-ICMA.*

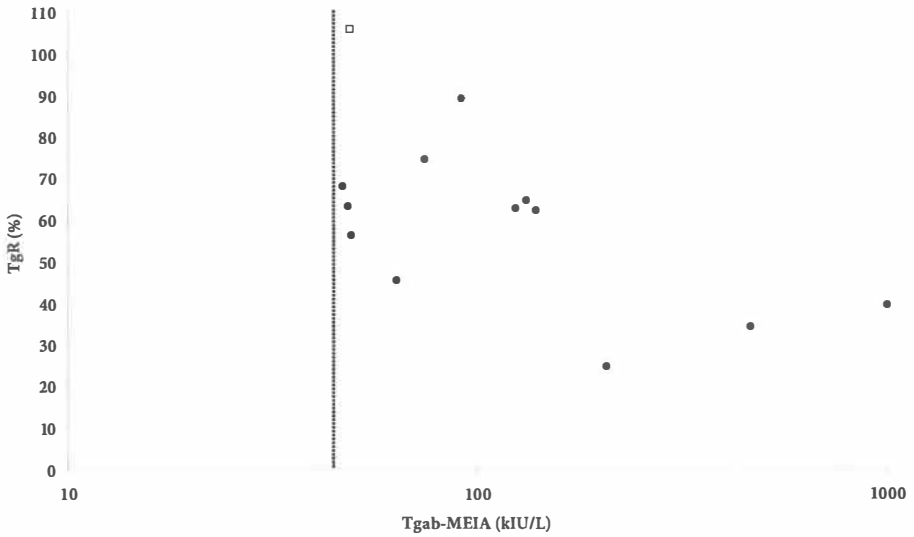

Figure 1C. *TgR in TgAb-MEIA positive sera.*

TgR in 13 TgAb-MEIA positive sera.
Cut-off value TgAb-MEIA positivity: 45 kilounits/L.
• *indicates sample with TgAb-positivity in both TgAb-ICMA and TgAb-MEIA.*
□ *indicates sample with TgAb- positivity in only TgAb-MEIA.*

Remeasurement of 6 TgAb-positive sera (patients 4,8,13,14,15 and 17 in Table 2) by Tg-RIA to determine whether TgR was falsely unaffected showed no RIA/ICMA discordance, thus favoring the outcome of the TgR results. The results for patient 8, with TgR within the reference interval, illustrate that despite TgAb positivity in both TgAb assays, serum Tg was measurable by the Tg-ICMA and seemed unaffected on the basis of a comparison with the Tg-RIA result (Table 2). Follow-up studies are needed to determine whether low TgAb positivity in sera with TgR within the reference interval indicates disease activity or represents signal noise, a distinction of major concern in clinical practice. The detection of TgAb in a patient means the loss of clinical utility of Tg measurements. In addition, the presence of supposed TgAb positivity might prompt unnecessary imaging and promote unnecessary patient concern. TgR measurements might be helpful in these particular cases.

We also performed Tg-RIA measurements in 9 of 10 sera that were positive for TgAbs in both assays and showed compromised TgR. In 3 cases (patients 1, 5, and 11), intermethod comparison provided no further evidence for interference in the serum Tg measurement, whereas in 6 cases (patients 2, 6, 7, 9, 10, and 12), RIA/ICMA discordance confirmed Tg interference. Remarkably, only 1 of these patients (patient 12) had known disease activity: the other patients with considerably high TgAb titers and compromised TgR had no evidence of disease and had been in follow-up for up to 29 years (range, 1-29 years). Several studies have

shown that persistence of TgAb positivity during long-term follow-up may be representative of persistent disease (5,13), whereas serum TgAb concentrations decrease or disappear in disease-free patients. Accordingly, TgAb positivity in conjunction with compromised TgR and ICMA/RIA discordance in these patients should alert the clinician. Serial TgAb measurements as surrogate tumor marker (10) and follow-up will show whether these patients really have persistent or recurrent disease.

In this study, we showed that testing for TgR by the Nichols Advantage TgR assay has value complementary to that of quantitative TgAb measurement in the detection of interference in Tg measurements, in particular in sera with low TgAb titers. Furthermore, this method can detect interference from TgAbs not detected by direct TgAb measurement or from other interfering substances, such as heterophilic antibodies. Further studies are needed to confirm the potential added value of this TgR assay. We would like to emphasize that the results observed with the Nichols Advantage TgR assay cannot be transposed to other TgR assays (5,6).

Acknowledgements

We thank J. Koerts and E. Heine for technical assistance and Nichols Institute Diagnostics for support. We thank Dr. C.A. Spencer for the Tg-RIA measurements.

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Chapter 4

A sensitive Tg assay or rhTSH stimulated Tg: what's the best in the long-term follow-up of patients with differentiated thyroid carcinoma?

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PLoS ONE 2007;2(8):e816

Abstract

Background: Sensitivity of thyroglobulin (Tg) measurement in the follow-up of differentiated thyroid carcinoma (DTC) can be optimized by using a sensitive Tg assay and rhTSH stimulation.
We evaluated the diagnostic yield of a sensitive Tg assay and rhTSH stimulated Tg in the detection of recurrences in the follow-up of DTC. Additionally the value of imaging techniques for the localization of recurrences was evaluated.
Methods: We included 121 disease free patients in long-term follow-up for DTC (median 10 years, range 1-34). Tg during thyroid hormone suppression therapy (Tg-on) and rhTSH stimulated Tg were measured with a sensitive Tg assay. Patients with rhTSH stimulated Tg ≥ 1.0 ng/ml underwent imaging with neck ultrasound, FDG-PET and post therapy I-131 whole body scan (WBS).
Results: Sensitive Tg measurement resulted in 3 patients with Tg-on ≥ 1.0 ng/ml, recurrence could be localized in 2 of them. RhTSH stimulation resulted in Tg ≥ 1.0 ng/ml in another 17 of 118 patients. Recurrence could be localized in only 1 additional patient (1 of 118 patients). Recurrence was localized by neck ultrasound in 1 of 3, by FDG-PET in 2 of 3 and by post therapy I-131 WBS in 2 of 3 patients.
Conclusions: In the detection of recurrences in DTC, rhTSH stimulation had very limited additional value in comparison to Tg-on measurement with a sensitive Tg assay. We consider this too low to justify rhTSH stimulation in all patients during long-term follow-up. Neck ultrasound, FDG-PET and post therapy I-131 WBS showed complementary value in localization of disease, but were only positive in a small fracture of all procedures.

Introduction

Although differentiated thyroid cancer (DTC) is characterized by an excellent prognosis after thyroidectomy and radioiodine ablation, recurrences occur often even many years after this initial therapy (1). Therefore, lifelong follow-up of DTC is recommended. The clinical and economical relevance of optimal follow-up with accurate diagnostic testing is crucial considering the large population of patients in lifelong follow-up for DTC world-wide.

Traditionally, the cornerstone of follow-up is serum thyroglobulin (Tg) measurement. Optimal sensitivity is reached when Tg is measured during thyrotropin (TSH) stimulation because TSH promotes Tg synthesis (2). TSH stimulation can be simply achieved by induction of hypothyroidism following thyroid hormone withdrawal. However, externally administered recombinant human TSH (rhTSH) has recently been proven to be an effective alternative to thyroid hormone withdrawal. It stimulates the release of Tg by thyroid remnants and metastatic lesions of DTC without inducing the poorly tolerated side effects of hypothyroidism

(3,4,5). Besides the availability of rhTSH, also the recent development of more sensitive Tg assays may considerably increase the sensitivity of Tg measurement to detect recurrent disease. New immunometric assays (IMA) have a functional sensitivity as low as 0.1 ng/ml (6), possibly allowing the detection of smaller amounts of thyroid tissue, even when TSH is suppressed (7).

The current European guidelines for the follow-up of DTC (8) recommend the use of a sensitive Tg assay that is standardized on the European reference standard (CRM-457) (9,10) with a functional sensitivity < 1.0 ng/ml. Additionally, the use of rhTSH for Tg measurement is recommended for the first evaluation 6-12 months after initial therapy to confirm the adequacy of thyroidectomy and radioiodine ablation (8,11,12). Although several studies (4,5) support the diagnostic accuracy of rhTSH stimulated Tg measurement at the time of this first evaluation, the optimal management of DTC patients concerning Tg measurement in the long-term follow-up phase is less clear. Some authors consider Tg measurement during thyroid hormone suppression therapy (Tg-on) sufficient for the detection of recurrences in low-risk patients as long as Tg remains undetectable (7,8,13). Others favour periodic rhTSH stimulated Tg measurement, arguing that tumor may exist in patients with an undetectable Tg-on (11,12). Prospective data about these issues are lacking. Accordingly, the recently published American Thyroid Association (ATA) management guidelines for patients with DTC state that the timing or necessity of subsequent rhTSH stimulated Tg testing is uncertain for those found to be free of disease (14).

Recently, Smallridge et al. (6) questioned if a Tg assay with improved sensitivity could eliminate the need for rhTSH stimulation when Tg during thyroid hormone suppression therapy is < 1.0 ng/ml. This retrospective study showed that when using a sufficiently sensitive Tg assay, these patients rarely have a rhTSH stimulated Tg > 2 ng/ml and only one of 80 patients had detectable disease. This recurrence was demonstrated by ultrasound despite numerous imaging studies. Additionally, the lack of localizable disease in a significant part of patients with detectable stimulated Tg, brings up for discussion, whether this stimulation is useful. The lack of evidence that the early detection of especially local disease will improve prognosis actualizes this question even more (15,16).

For the detection of recurrent disease several imaging methods are used. Neck ultrasound has established a fixed place in the follow-up of DTC, particularly for the detection of cervical lymph node metastasis (17). The timing and the method of choice for additional imaging is less clear. Applied methods are post therapy I-131 whole body scan (WBS), computed tomography (CT) of the neck and chest, 18-F Fluorodeoxyglucose Positron Emission Tomography (FDG-PET), and magnetic resonance imaging (MRI).

In this study, we evaluated the introduction of a highly sensitive Tg assay (18) and the additional value of rhTSH stimulation, for the detection of recurrences in disease free patients in long-term follow-up for DTC. Additionally, we evaluated the value of different imaging techniques including neck ultrasound, FDG-PET scan and post therapy I-131 WBS in the localization of recurrent disease in Tg positive patients.

METHODS

Study Population

All patients who were treated and followed for DTC in the University Medical Centre Groningen (UMCG) between 1978 and 2003 and were disease free were eligible for participation. Disease free was defined as no clinical evidence of recurrent or persistent DTC and undetectable Tg-on for at least 1 year. This Tg level had been routinely measured by an immunoradiometric assay (CIS Bio International, Gif-sur-Yvette, France) with a detection limit of 1.5 ng/ml for many years. Exclusion-criteria were age under 18 years or above 75 years, pregnancy and severe psychiatric illness. Additionally, patients testing positive for Tg antibodies were excluded.

All patients had undergone initial treatment consisting of total thyroidectomy, followed by radioiodine ablation therapy. Additional treatment, such as lymph node dissection and additional I-131 therapy was performed when indicated. Routine follow-up included visits at the outpatient clinic every four months in the first two years, and thereafter annually. At each visit physical examination of the neck, Tg-on and TSH measurement were performed. Patients used a suppressive dose of levothyroxin. All patients gave written informed consent to participate in the study, which was approved by the medical ethical review committee of the University Medical Centre Groningen.

Study design

At baseline, Tg-on was measured with a new sensitive Tg assay (see "Serum measurements" section) in all patients. Subsequently, all patients underwent rhTSH stimulated Tg measurement. Patients with rhTSH stimulated Tg ≥ 1.0 ng/ml underwent additional imaging including FDG-PET scanning, neck ultrasound and post therapy I-131 WBS to detect recurrent disease. After 3 months Tg-on and rhTSH stimulated Tg measurement were repeated.

RhTSH stimulated Tg measurement

RhTSH (Thyrogen, Genzyme Corporation, Cambridge, MA) was administered intramuscularly (i.m) at a dose of 0.9 mg once a day for two consecutive days, while maintaining thyroid hormone suppression therapy. Seventy-two hours after the second rhTSH injection, Tg and TSH were measured.

Imaging studies and radioiodine treatment

For detection of recurrent disease, patients underwent FDG-PET, ultrasound examination of the neck (with fine needle aspiration when indicated) and treatment with 150 mCurie I-131 followed by a post therapy I-131 WBS.

FDG-PET scan was performed during thyroid hormone withdrawal, using an ECAT HR+ camera (Siemens/CTI, Knoxville, TN). Patients fasted overnight before the investiga-

tion. Ninety minutes after intravenous injection of 5 MBq/kg of FDG, a 2-D whole-body image was acquired from top of the skull to the knees. Images were reconstructed using iterative methods with attenuation correction. Emission time was 5 minutes and transmission time was 3 minutes.

Ultrasound of the neck was performed by an experienced and dedicated radiologist using a Siemens machine with a linear 13 MHz transducer, with fine needle aspiration of suspicious lymph nodes or masses. Lymph nodes with short axis ≥ 10 mm and/or round oval shape, unsharp borders, inhomogeneous pattern (in particular calcifications or cystic changes), absence of echogenic hilus or hypoechoic pattern (17,19,20) were biopsied with percutaneous fine needle aspiration. In case of a hot spot in the neck on the FDG-PET scan, this information was passed to the radiologist who tried to puncture this specific node.

Post therapy I-131 WBS was performed with a two-headed gammacamera (Multispect 2, Siemens) with a high-energy collimator. We acquired three to four 10-minute adjacent spot views covering the whole body in anterior and posterior views. When necessary, additional views were obtained. The post therapy I-131 WBS was performed 10 days after the administration of 150 mCurie I-131. All these imaging procedures were performed within two weeks.

Additional imaging, including MRI and CT, was performed to confirm positive findings on either post therapy I-131 WBS or FDG-PET scan. Levothyroxin was stopped six weeks before radioiodine treatment and replaced by triiodothyronine until two weeks before radioiodine treatment. Levothyroxin was restarted after the treatment. A low iodine diet was followed during one week before treatment. Tg and TSH were measured six weeks after thyroid hormone withdrawal (Tg-off), on the day of the I-131 treatment.

To evaluate the effect of radioiodine treatment, we repeated Tg-on and rhTSH stimulated Tg measurement four months after treatment with 150 mCurie I-131.

Evaluation of imaging and final disease status

All imaging, radiological and nuclear images were evaluated and compared with previous scans by an independent expert panel consisting of endocrinologists, nuclear medicine physicians and a head-neck surgeon, aided by a radiologist when required. Disease status of each patient was assessed and categorized as "no recurrence localized" or "recurrence localized". "Recurrence localized" implied one or more abnormal imaging studies strongly suggestive of recurrent or metastatic thyroid carcinoma. "No recurrence localized" implied negative radiological and nuclear imaging. Subsequently, the expert panel determined the therapeutic consequences of the findings.

Serum measurements

Before inclusion in this study, during routine follow-up, Tg was measured by an immunoradiometric assay with functional sensitivity of 1.5 ng/ml (Cis Bio International, Gif-

sur-Yvette, France). During the study, Tg was measured by a more sensitive assay (Nichols Advantage® Tg assay, Nichols Institute Diagnostics, San Clement, CA, USA). This is a fully automated chemiluminescence sandwich immunoassay with functional sensitivity of 0.6 ng/ml and calibrated against the CRM-457 reference preparation (18).

TSH was measured by a time-resolved fluoroimmunoassay using the DELFIA system (PerkinElmer Life Sciences, Turku, Finland) with a detection limit of 0.003 mU/l. Tg antibodies (TgAb) were measured by a chemiluminescence immunoassay (Nichols Advantage, Nichols Institute Diagnostics, San Clement, CA, USA) with a cut-off value for TgAb positivity of 2 IU/ml (21). All serum measurements were performed in the same institution (UMCG).

Statistical analysis

Data are expressed as median and range. The differences in Tg and TSH before and after radioiodine treatment were analysed using the Wilcoxon test for paired data. For statistical reasons, Tg values < 0.6 were considered to be equal to 0.6 ng/ml and TSH values < 0.003 were considered to be equal to 0.003 mU/L in this test. P-values of less than 0.05 were considered to indicate statistical significance. Statistical analysis was performed using SPSS version 10.0 software (SPSS, Inc., Chicago, IL.).

Results

Study patients

Hundred twenty-one patients with DTC (female 76%, median age 54 years, median follow-up 10 years (range 1-34) after initial surgery) were studied (Table 1). Patients were divided in three groups on the basis of Tg-on result.

Table 1. Disease characteristics

Characteristic	All patients N=121	Patients with undetectable Tg-on N=115	Patients with Tg-on 0.6-1.0 ng/ml N=3	Patients with Tg-on ≥ 1.0 ng/ml N=3
Sex –no. (%)				
Female	92 *(76)*	89 *(77)*	2 *(67)*	1 *(67)*
Male	29 *(24)*	26 *(13)*	1 *(33)*	2 *(33)*
Age[a] (yrs)	54 *(43-61)*	54 *(43-61)*	49 *(33-51)*	56 *(31-64)*
Histology –no. (%)				
Papillary	86 *(71)*	81 *(70)*	3 *(100)*	2 *(67)*
Follicular	29 *(24)*	29 *(25)*	0	0
Hürthle cell	6 *(5)*	5 *(4)*	0	1 *(33)*
Follow-up[a] (yrs)	10 (6-16)	10 (6-16)	8 (5-27)	16 (5-23)
TNM-classification[b] –no. (%)				
T1-T3	100 *(82)*	96 *(84)*	3 *(100)*	1 *(33)*
T4	3 *(3)*	2 *(2)*	0	1 *(33)*
Tx	18 *(15)*	17 *(15)*	0	1 *(33)*
N0	85 *(70)*	84 *(73)*	1 *(33)*	0
N1	32 *(27)*	27 *(24)*	2 *(67)*	3 *(100)*
Nx	4 *(3)*	4 *(4)*	0	0
M0	120 *(99)*	114 *(99)*	3 *(100)*	3 *(100)*
M1	1 *(1)*	1 *(1)*	0	0
TNM-stage[b] –no. (%)				
<45 years				
stage I	72 *(60)*	68 *(59)*	3 *(100)*	1 *(33)*
stage II	0	0	0	0
>45 years				
stage I	5 *(4)*	5 *(4)*	0	0
stage II	26 *(21)*	26 *(23)*	0	0
stage III	11 *(9)*	9 *(8)*	0	2 *(67)*
stage IV	1 *(1)*	1 *(1)*	0	0
unknown	6 *(5)*	6 *(5)*	0	0
Risk-group[c] –no. (%)				
Low-risk	103 *(85)*	99 *(86)*	3 *(100)*	1 *(33)*
High-risk	12 *(10)*	10 *(9)*	0	2 *(67)*
Unknown	6 *(5)*	6 *(5)*	0	0

[a] Median with interquartile range (25th and 75th centile) in the groups "All patients, n=121" and "Patients with undetectable Tg-on", N=115". Median and range in the groups "Patients with Tg-on 0.6-1.0 ng/ml, N=3"and "Patients with Tg-on ≥ 1.0, N=3".

[b] TNM-classification and staging according to Hermanek & Sobin, 1992 (34).

[c] Low-risk patients are stage I disease if younger than 45 years or Stage I or II if older than 45 years.

Group 1: Patients with Tg-on ≥ 1.0 ng/ml

In three patients Tg-on was ≥ 1.0 ng/ml (Table 2). As expected, in these three patients Tg after rhTSH was also ≥ 1.0 ng/ml. Imaging resulted in the localization of a recurrence in two of them. In patient A (Tg-on 1.1 ng/ml) no recurrence could be identified on FDG-PET scan, neck ultrasound, post therapy I-131 WBS or MRI scan of the neck region (Table 3). In patient B (Tg-on 1.3 ng/ml), recurrence was located in the lower jugular region and identified on neck ultrasound, MRI and CT scan. There was no I-131 uptake. Selective neck dissection was performed and three malignant lymph nodes were removed. Patient C (Tg-on 2.8 ng/ml)

had an extensive paravertebral/mediastinal recurrence, identified on FDG-PET scan, post therapy I-131 WBS, and a subsequent MRI, CT scan and octreotide scintigram. This tumor was inoperable and not amenable to radioiodine or octreotide therapy. External radiotherapy with palliative intention was started. Patient died from respiratory insufficiency due to the consequences of metastatic thyroid carcinoma, eleven months after the identification of recurrent disease.

Tg-on measurement (Table 2) was repeated 4 months after radioiodine treatment (before neck dissection in patient B and the start of radiotherapy in patient C, patient A refused Tg measurement). Tg-on was lower but remained detectable in both patients (Table 3). Only in patient B, rhTSH stimulated Tg measurement was repeated after radioiodine therapy (patient A refused and patient C was not stimulated because of extensive disease). RhTSH stimulated Tg was 6.7 ng/ml before radioiodine therapy and 5.3 ng/ml after radioiodine therapy.

Group 2: Patients with Tg-on 0.6-1.0 ng/ml

Three patients (Table 2) had detectable Tg-on levels between 0.6 and 1.0 ng/ml (0.76, 0.81 and 0.99 ng/ml). After rhTSH stimulation Tg was undetectable in the first patient and rose to 1.3 and 8.6 ng/ml in the two other patients. These two patients were referred for imaging. In none of them recurrence was localized (Table 4).

Four months after radioiodine treatment Tg-on and rhTSH stimulated Tg were measured again (Table 4). Tg-on after radiodine treatment remained detectable in one of both patients (2.6 ng/ml). At the second rhTSH stimulated Tg measurement, Tg remained detectable in both patients (0.96 and 10.0 ng/ml).

Group 3: Patients with undetectable Tg-on (< 0.6 ng/ml)

Tg-on was undetectable in 115 patients. After rhTSH stimulation, Tg became detectable in 19 patients (Table 2). In 15 patients (13%) rhTSH stimulated Tg was ≥ 1.0 ng/ml (median 1.6 ng/ml, range 1.0-5.4). Imaging was performed in 14 out of these 15 patients with undetectable Tg-on and rhTSH stimulated Tg ≥ 1.0 ng/ml. One patient refused imaging because of pregnancy wish. After evaluation of all images, recurrence was localized in one of 14 patients (Table 5). Recurrence was localized in patient F and was located in the right supraclavicular fossa and identified on FDG-PET scan, post therapy I-131 WBS and MRI scan. The suspicious lesion was resected and histopathological analysis showed a lymph node metastasis of papillary thyroid carcinoma. In the remaining 13 patient no recurrence could be localized.

Four months after radioiodine treatment (and before surgery in patient F), Tg-on and rhTSH stimulated Tg were measured again (Table 2). Tg-on had become detectable in 1 of 14 patients, Tg and TSH levels did not significantly differ (p=0.4 and 0.7) compared to the situation before radioiodine treatment. At the second rhTSH stimulated Tg measurement, Tg remained detectable in 13 of 14 patients but was significantly lower (p=0.005) than before radioiodine treatment while no difference in TSH was found (p=0.084).

Table 2. Serum Tg and TSH levels

	Patients with Tg-on ≥ 1.0 ng/ml[a] (N=3)	Patients with Tg-on 0.6-1.0 ng/ml[a] (N=3)	Patients with Tg-on < 0.6 ng/ml[g] (N=115)
Tg-on (ng/ml)[b]	1.3 (1.1-2.8)	0.81 (0.76-0.99)	<0.6
TSH (mU/l)	0.04 (0.004-0.075)	0.014 (0.003-2.4)	0.048 (0.017-0.31)
Tg after rhTSH (ng/ml)	5.3 (4.5-6.7)	1.3 (<0.6-8.6)	<0.6 (<0.6-<0.6)
TSH (mU/l)	13 (9.2-19)	7.4 (14.0-15.0)	14.0 (9.8-20.0)
Tg-off (ng/ml)[c]	8.1 (3.5-10.0)	2.6/20.0[e]	3.75 (1.65-6.78)[f]
TSH (mU/l)	16.0 (21.0-46.0)	48.0/50.0	46.5 (35.5-53.5)
Tg-on (ng/ml), 4 months after radioiodine treatment	1.0 (0.84-1.9)	<0.6/2.6[e]	<0.6 (<0.6-<0.6)[f]
TSH (mU/l)	0.018 (0.014-0.022)	0.019/0.11	0.03 (0.008-0.46)
Tg after rhTSH (ng/ml), 4 months after radioiodine treatment	5.3[d]	0.96/10.0[e]	1.35 (0.99-1.95)[f]
TSH (mU/l)	26	17/26	14.5 (9.9-21.5)

[a] Median with range.
[b] Tg-on: Tg during thyroid hormone suppression therapy.
[c] Tg-off: Tg after 6 weeks thyroid hormone withdrawal.
[d] N = 1: RhTSH stimulated Tg measurement, 4 months after radioiodine treatment was performed in one of three patients. One patient refused, the second patient was not stimulated because of extensive disease.
[e] N = 2: RhTSH stimulated Tg was ≥ 1.0 ng/ml in 2 patients, these patients were referred for imaging.
[f] N = 14: RhTSH stimulated Tg was ≥ 1.0 ng/ml in 15 patients, imaging was performed in 14 patients. In one patient imaging was not performed because of pregnancy wish.
[g] Median with interquartile range (25th and 75th centile).

Diagnostic yield of imaging tests

Imaging studies were performed in 19 of 20 patients with rhTSH stimulated Tg ≥ 1.0 ng/ml (one patient refused because of pregnancy wish). All these patients underwent neck ultrasound, FDG-PET scan and post therapy I-131 WBS. Additional imaging including MRI, CT and octreotide scanning was performed when better anatomical localization was needed or when results were contradicting. Only in three patients recurrence could be localized.

In patient B (Table 3) recurrence was localized in the neck and was initially detected by neck ultrasound. FDG-PET scan and post therapy I-131 WBS were negative. Exact anatomical localization was achieved by CT and MRI. Patient C (Table 3) had extensive metastatic disease, which was visualized by nuclear medicine methods (FDG-PET, radioiodine imaging, octeotride scintigraphy) as well as CT and MRI. Patient F (Table 5) with a supraclavicular lesion had a negative ultrasound and positive FDG-PET, post therapy I-131 WBS and MRI.

Table 3. Patients with Tg-on ≥ 1.0 ng/ml

Pt	Age/Sex[a]	Histology[b]	TNM[c]	Risk group[c]	Follow- up	Tg-on[d,e]	Tg after rhTSH[e]	Tg-off[e,f]	Tg-on 4 months after I-131 therapy[e]	Tg after rhTSH 4 months after I-131 therapy[e]	Evaluation of imaging	Final disease status[h]	Therapeutic consequences
A	56/M	Pap	2 1 0	Low-risk	23	1.1	4.5	8.1	NP[g]	NP	Negative	NRL	None
B	31/F	Pap	4 1 0	Low-risk	5	1.3	6.7	10.0	0.84	5.3	**Neck lesion:** identified on neck US, MRI and CT	**Recurrence**	Surgical exploration
C	64/M	Hürthle	x 1 0	High-risk	16	2.8	5.3	4.7	1.9	NP[g]	**Mediastinal/ paravertebral lesion:** identified on FDG-PET, posttherapy I-131 WBS, CT, MRI, and Octreotide.	**Recurrence**	Radio-therapy palliation

Table 4. Patients with Tg-on 0.6-1.0 ng/ml and rhTSH stimulated Tg ≥ 1.0 ng/ml

Pt	Age/Sex[a]	Histology[b]	TNM[c]	Risk group[c]	Follow- up	Tg-on[d,e]	Tg after rhTSH[e]	Tg-off[e,f]	Tg-on 4 months after I-131 therapy[e]	Tg after rhTSH 4 months after I-131 therapy[e]	Evaluation of imaging	Final disease status[h]	Therapeutic consequences
D	51/F	Pap	1 1 0	Low-risk	27	0.81	1.3	2.6	<0.6	0.96	Negative	NRL	None
E	33/M	Pap	2 1 0	Low-risk	8	0.99	8.6	20	2.6	10.0	Negative	NRL	None

Table 5. Patients with undetectable Tg-on and rhTSH stimulated Tg ≥ 1.0 ng/ml

Pt	Age/Sex[a]	Histology[b]	TNM[c]	Risk group[c]	Follow- up	Tg-on[d,e]	Tg after rhTSH[e]	Tg-off[e,f]	Tg-on 4 months after I-131 therapy[e]	Tg after rhTSH 4 months after I-131 therapy[e]	Evaluation of imaging	Final disease status[h]	Therapeutic consequences
F	58/M	Pap	2 0 0	Low-risk	12	<0.6	3.9	4.8	<0.6	1.9	**Supraclavicular lesion:** identified on FDG-PET, posttherapy I-131 WBS, MRI	**Recurrence**	Surgical exploration
G	55/F	Pap	2 1 0	High-risk	3	<0.6	2.8	6.7	<0.6	1.6	Negative	NRL	None
H	50/M	Foll	2 0 0	Low-risk	10	<0.6	3.1	11.0	0.6	2.1	Negative	NRL	None
I	39/M	Pap	2 1 0	Low-risk	4	<0.6	3.0	8.4	<0.6	2.5	Negative	NRL	None
J	55/F	Pap	2 0 0	Low-risk	10	<0.6	1.2	2.3	<0.6	1.3	Negative	NRL	None
K	43/F	Pap	2 0 0	Low-risk	17	<0.6	1.6	6.0	<0.6	0.79	Negative	NRL	None
L	36/F	Pap	2 1 0	Low-risk	16	<0.6	2.2	NP[g]	<0.6	NP[g]	No imaging because of pregnancy wish	–	–
M	53/F	Pap	1 0 0	Low-risk	3	<0.6	1.0	1.8	<0.6	<0.6	Negative	NRL	None
N	60/M	Pap	4 1 0	High-risk	5	<0.6	1.0	1.7	<0.6	1.0	Negative	NRL	None
O	68/M	Pap	1 1 0	High-risk	16	<0.6	1.4	1.0	<0.6	1.3	Negative	NRL	None
P	55/M	Pap	2 1 0	Low-risk	18	<0.6	1.2	1.5	<0.6	1.2	Negative	NRL	None
Q	48/F	Pap	2 0 0	Low-risk	15	<0.6	5.4	2.7	<0.6	4.3	Negative	NRL	None
R	42/F	Pap	2 0 0	Low-risk	5	<0.6	1.4	5.1	<0.6	1.4	Negative	NRL	None
S	46/F	Pap	4 0 0	Low-risk	18	<0.6	3.9	7.0	<0.6	1.9	Negative	NRL	None
T	60/M	Fol	1 1 0	Low-risk	21	<0.6	1.1	0.85	<0.6	0.96	Negative	NRL	None

Table 3, 4, 5.

[a] M:male, F:female.

[b] Pap: papillary, Foll: follicular, Hürthle: Hürthle cell.

[c] TNM classification and risk group staging (34).

[d] Tg during thyroid hormone suppression therapy.

[e] All Tg results in ng/ml.

[f] Tg after thyroid hormone withdrawal.

[g] NP: not performed.

[h] Recurrence: recurrence localized, NRL: no recurrence localized.

Discussion

This prospective study showed that the introduction of a new sensitive Tg assay for clinical disease free patients resulted in the localisation of 2 recurrences (1.8%) in a cohort of 121 patients considered to be in remission. The additional yield of rhTSH stimulation in these patients was 1 additional localized recurrence (1 of 118 patients, 0.8%). We consider this too low to justify rhTSH stimulation in all patients. These results confirm the retrospective data recently presented by Smallridge et al. (6).

Although the presence of the established risk factors result in a reduced life expectancy (22), also initial low-risk patients can die from thyroid cancer (23), illustrating that distinction between high and low-risk is limited (24). Therefore in this study, we included patients irrespective of prognostic factors influencing risk of recurrence. Additionally, most recurrences occur within the first decade after initial therapy, but up to one third of recurrences occur in the subsequent years. Recurrences are described even more than 40 years after initial diagnosis (1). Therefore, lifelong follow-up is advised (8). We included patients regardless of follow-up duration. By doing so, this study population consisted of a mixture of low-risk and high-risk patients and variable follow-up duration, reflecting the variety of patients in follow-up for DTC in daily clinical practice (25) and results of this study are applicable to all patients with DTC in follow-up for DTC.

Tg measurement is the cornerstone in the follow-up of DTC but accurate measurement of Tg is technically challenging. An important requirement of Tg assays is a functional sensitivity low enough to detect small amounts of thyroid tissue when TSH is suppressed (7). The importance and surplus value of a sensitive Tg assay has been shown in this study. Two patients with recurrent disease could be identified solely on the basis of Tg-on levels ≥ 1.0 ng/ml by using a sensitive Tg assay. In 2 of 3 patients, with Tg-on ≥ 1.0 ng/ml recurrent disease could be localized so diagnostic yield of imaging was high when using 1.0 ng/ml as cut-off. Tg-on in these patients had been undetectable by the conventional assay, so formerly rhTSH stimulated Tg measurement would have been needed to identify these patients. These patients are illustrative that optimizing sensitivity of Tg assays, may obviate the need for rhTSH stimulated Tg measurement in the future follow-up of DTC (26).

In one patient with undetectable Tg-on, recurrent disease was found. Only in this patient (1 of 121 patients) rhTSH stimulated Tg measurement had additional diagnostic yield in the detection of recurrent disease. Clearly, this very limited result of rhTSH testing does not validate the introduction of routine rhTSH stimulated Tg measurement in the follow-up of DTC. Moreover, regular serial Tg-on measurement with a sensitive Tg assay anyhow would have identified this solely patient, since the change in Tg over time is more informative than a single Tg determination (27). Tg-on will increase during serial Tg-on measurement (28,29) when recurrent disease is actually present.

Zanotti-Fregonara et al. (30), also evaluated the utility of rhTSH stimulation. Their results endorse the limited value of periodic rhTSH stimulation in patients with stage I thyroid cancer. In contrast, they recommend rhTSH stimulation in higher-risk patients because of positive Tg levels after rhTSH in 4 of 35 high-risk patients (11%). However, two of these patients already had detectable Tg-on levels. In only one patient, recurrence was localized 10 months after the last I-131 therapy, and according to our definition this patient could not be considered as in remission. Results of our study do not support the use of rhTSH stimulation in the long-term follow-up of high-risk patients. Recurrent disease was localized in one low-risk patient with Tg only detectable after rhTSH stimulation (patient F) and in one low-risk and in one high-risk patient with detectable Tg-on (patient B and C respectively).

Uncertainty exists about the clinical value of low but detectable Tg-on values in sensitive Tg assays. In the present study a small number of patients had Tg-on levels between 0.6 and 1.0 ng/ml. The rise in Tg after rhTSH to ≥ 1.0 ng/ml in 2 of these 3 patients indicated residual thyroid tissue and not an assay artefact (31). Nevertheless, recurrent disease could not be localized. This illustrates that the sensitivity of Tg measurement currently exceeds the sensitivity of the available imaging techniques and therefore careful watching of the slope of Tg-on is recommended. The optimal timing of imaging needs to be ascertained in future studies. Extensive imaging when Tg-on in a sensitive assay rises above a certain cut-off level will be far more efficient, preventing needless patient burden and medical costs.

In the present study, imaging including post therapy I-131 WBS, neck ultrasound and FDG-PET was performed in all patients suspected of recurrent disease. Neck ultrasound is considered the most sensitive method to detect local recurrence, although it is not specific and is an operator-dependent procedure (8,32). In contrast, radioiodine scanning has high specificity for recurrences of differentiated thyroid cancer but considerably low sensitivity (32). Particularly in radioiodine negative differentiated thyroid cancer, FDG-PET is useful and has both high sensitivity and specificity (33). Results of this study showed that these three imaging methods are complementary in the detection of recurrent disease. Nevertheless, additional imaging including CT and MRI scanning was needed to provide better anatomical localization of lesions. This result illustrates that the fusion of anatomy and metabolism by the recently introduced integrated PET/CT systems, is a promising technique (32,33).

Finding a low or undetectable Tg after rhTSH stimulation could be considered as a reassurance to patients that truly no disease activity is present. In the present study, Tg was < 1.0 ng/ml after rhTSH in the vast majority (87%) of patients. Actually, this result only confirmed the already known absence of disease in these patients with undetectable Tg-on. In this group of patients, rhTSH stimulation is an expensive, unnecessary diagnostic test. Moreover, these data underscore the adequacy of undetectable Tg-on confirming the absence of disease and contradict the opinion that "an undetectable serum Tg measured during thyroid hormone suppression is often misleading in a large proportion of patients with

residual DTC" (7). We did not routinely use neck ultrasound during follow-up so we could have missed small lymph node metastases in these patients. For it is known that lymph node metastases can be detected by neck ultrasound in patients with both undetectable Tg-on and undetectable rhTSH stimulated Tg or Tg-off (16,17). This is the reason why the combination of Tg measurement and neck ultrasound is now becoming the standard of care, although it is still controversial whether the early detection of generally very small lymph node metastases will improve prognosis (15,16).

In conclusion, Tg measurement with a sensitive Tg assay has an additional diagnostic yield in the detection of recurrent disease in patients in follow-up for DTC and practically obviates the need for rhTSH stimulated Tg measurement. Long-term follow-up of DTC can safely be based on serial Tg-on measurement with a sensitive Tg assay and additional diagnostic tests should be performed only when Tg-on rises above an established cut-off level. This will result in a limited follow-up protocol, warranting the detection of recurrences of DTC and reducing patient burden and medical costs.

Acknowledgements

This study was funded by an effectiveness grant from the University Medical Center Groningen. The funding source had no role in the study design, data collection, data analysis and interpretation or writing of the report.

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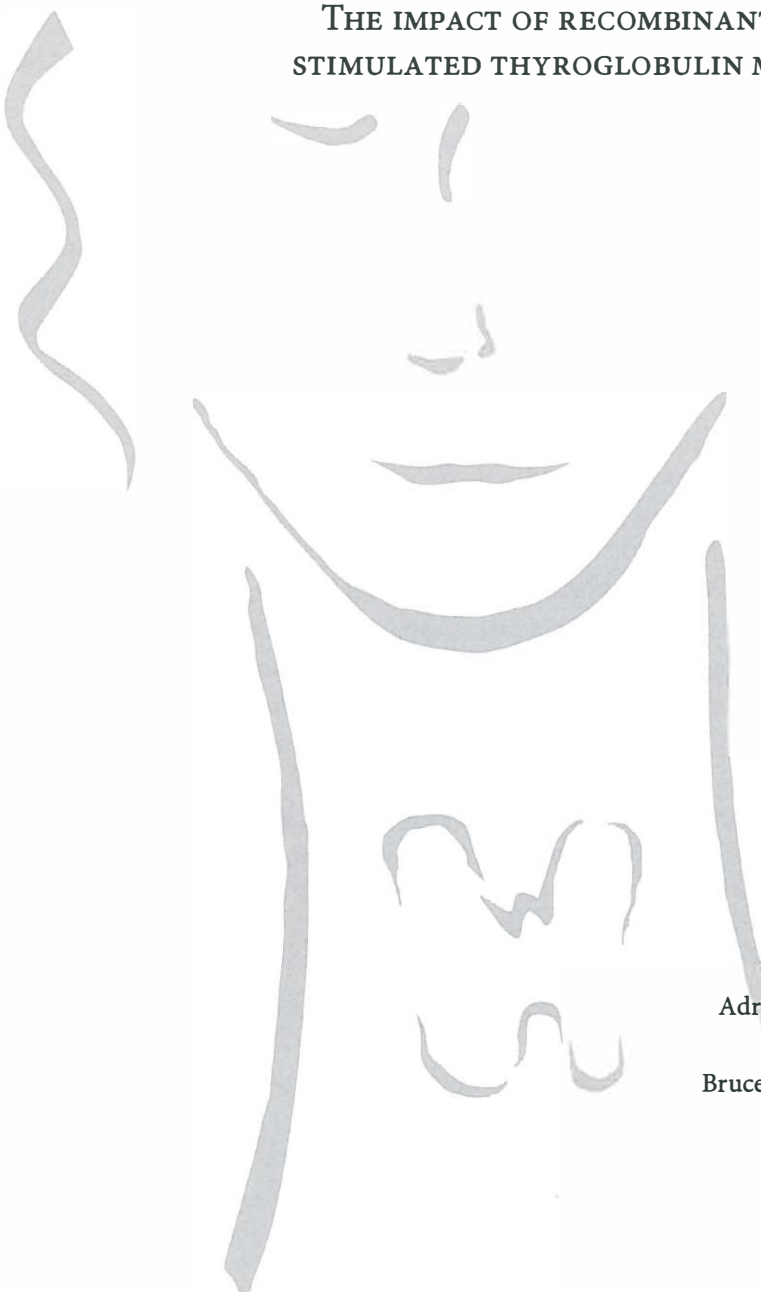
Chapter 5

Quality of life in patients in long-term follow-up for differentiated thyroid carcinoma

The impact of recombinant human TSH stimulated thyroglobulin measurement



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Abstract

Introduction: Knowledge of the quality of life (QOL) in patients in follow-up for differentiated thyroid cancer (DTC) is limited. Moreover, the impact of recombinant human TSH stimulated thyroglobulin (rhTSH-Tg) measurement, a monitoring method in the follow-up of DTC, on QOL is unknown. RhTSH-Tg includes the measurement of Tg, a tumor marker in the follow-up of DTC, after two consecutive injections of rhTSH. We assessed QOL in patient in long-term follow-up for DTC and the impact of rhTSH-Tg measurement and subsequent diagnostic procedures on QOL in these patients.

Methods: In 121 clinically disease free patients in long-term follow-up for DTC, Tg during thyroid hormone suppression therapy (Tg-on) and rhTSH-Tg were measured with a newly introduced sensitive assay. Patients with rhTSH -Tg ≥ 1.0 ng/ml (Tg + patients) underwent additional imaging. The RAND-36 questionnaire was only completed at baseline. Anxiety items of the Hospital Anxiety and Depression scale (HADS), the General Health Questionnaire (GHQ) and Cancer Worries (CW) were completed at baseline and after being informed about rhTSH-Tg result. Additionally, Tg + patients and a sex- and age-matched subset of Tg – patients (rhTSH-Tg < 1.0 ng/ml) completed these questionnaires after being informed about imaging results and subsequent conclusions about their disease status.

Results: RhTSH-Tg measurement resulted in 101 Tg – and 20 Tg + patients. Imaging showed recurrence in 3 of 19 Tg + patients. Two of these three patients could have been identified solely by Tg-on. At baseline, DTC patients showed impaired quality of life compared with the general population (RAND-36). For Tg + patients, anxiety, psychological distress and CW significantly increased after being informed about Tg result. Moreover, CW remained increased in Tg + patients after being informed about disease status compared with Tg – patients, even though additional imaging showed no recurrence in most of them.

Conclusion: Patients in long-term follow-up for DTC showed reduced QOL. Additionally, notification of a positive rhTSH-Tg has a negative effect on QOL. Cancer worries remained increased compared with Tg – patients, despite of negative imaging. The low yield of rhTSH testing and its negative impact on QOL justifies withholding this test during long-term follow-up.

Introduction

Differentiated thyroid carcinoma (DTC) generally has a good prognosis with 10-year survival rates as high as 90% (1). In the follow-up of DTC, the aim is the early detection of recurrent disease to prevent local incurable disease and mortality. Up to 20% of patients develop recurrent disease and late recurrences can occur even after 15-20 years (2-4). Therefore, life-

long follow-up is recommended. The measurement of thyroglobulin (Tg) as a tumor marker is the cornerstone in follow-up.

Traditionally, primary outcome measures in cancer follow-up are overall survival and disease-free survival (5,6). Accordingly, in the follow-up of thyroid cancer the attention is mainly focused at developing optimal monitoring methods to detect recurrent disease, and improving the sensitivity of the tumor marker (Tg) measurement. However, the effect of different monitoring methods on the psychological health of patients has received only limited attention. Especially because follow-up of thyroid cancer is lifelong, recognizing the impact of monitoring on psychological health is important.

After initial therapy, consisting of (near) total thyroidectomy and radioiodine ablation therapy, thyroid hormone suppression therapy is initiated to prevent hypothyroidism and to diminish the risk of recurrent disease. During follow-up, sometimes thyroid hormone withdrawal is needed to optimize sensitivity of diagnostic radioiodine scanning or Tg measurement. The negative impact of thyroid hormone withdrawal on quality of life (QOL) is well-documented. The induced hypothyroidism causes a significant deterioration in patients QOL (7). The introduction of recombinant human TSH (rhTSH) allows sensitive diagnostic testing comparable to thyroid hormone withdrawal (8) without the necessity to stop thyroid hormone replacement. The use of rhTSH prevents the dramatic decrease in quality of life related to hormone withdrawal (9,10). However, whether this TSH stimulation, either by rhTSH or thyroid hormone withdrawal is necessary in the long-term follow-up of DTC is unclear (11). Especially with the increasing availability of the high sensitive Tg assays, Tg measurement during thyroid hormone suppression therapy (Tg-on) might be sufficient.

Although the negative influence of thyroid hormone withdrawal on QOL is avoided, monitoring with rhTSH stimulated Tg measurement or Tg-on measurement might still influence QOL, and specifically the psychological dimension of QOL. Every follow-up test used, is inevitably hampered by the occurrence of false positive test results. This can lead to unnecessary additional testing and physical and psychological harm. In an earlier study, we showed that rhTSH stimulated Tg measurement resulted in a significant amount of patients with rhTSH-Tg > 1.0 ng/ml, suspect for recurrent disease. However, the diagnostic yield of extensive imaging in these patients was very limited (12). The use of rhTSH stimulated Tg measurement in 121 patients, resulted in the localization of 1 additional recurrence, compared with Tg-on measurement with a sensitive Tg assay. When using sensitive Tg assays, the clinical significance of low detectable Tg levels is unclear and unnecessary testing and treatment is likewise a critical issue (13). Data about the impact of a positive (rhTSH stimulated) Tg test and subsequent diagnostic testing on psychological health are lacking.

Therefore, we examined the quality of life in clinically disease free patients in long-term follow-up for DTC as well as the impact of rhTSH stimulated Tg measurement and the subsequent diagnostic procedures on psychological distress, anxiety and cancer worries in these patients.

METHODS

Study population and study procedure

Clinically disease free patients in follow-up for DTC, were recruited from the outpatient clinic of the Department of Endocrinology of the University Medical Centre Groningen (UMCG), as earlier described (12) (Table 1). Patients were studied with questionnaires at three time points: at baseline after explaining the study procedure (T1), after being reported the result of rhTSH stimulated Tg measurement and the diagnostic consequences (T2) and after being informed of the results of all imaging and eventual therapeutic consequences of the findings (T3). At T1 and T2 all patients were studied. At T3, all Tg positive (19 Tg +) patients who received additional testing were studied and compared with a sex- and age-matched control group of Tg negative patients (36 Tg – patients) who did not receive diagnostic testing.

The study protocol with rhTSH stimulated Tg measurement and subsequent diagnostic imaging have been described previously (12). Figure 1 presents the flowchart of this study. In short, Tg during thyroid hormone suppression therapy (Tg-on) and rhTSH stimulated Tg were measured with a sensitive Tg assay (14). For rhTSH stimulated Tg measurement, patients received 0.9 mg rhTSH (Thyrogen, Genzyme Corporation, Cambridge, MA) by intramuscular injection on day 1 and 2, on day 5 thyroglobulin was measured. Patients with rhTSH stimulated Tg ≥ 1.0 ng/ml underwent imaging with neck ultrasound, FDG-PET and post therapy I-131 WBS.

All patients gave informed consent and the study procedures were approved by the medical ethical review committee of the University Medical Centre Groningen.

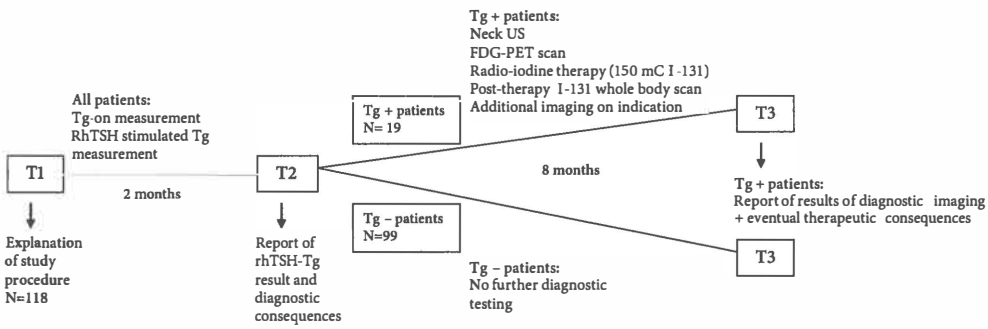

Figure 1. *Flow-chart of the study*

Measurements

Health related quality of life (HRQOL), psychological distress, anxiety and cancer worries were assessed by the use of questionnaires which were validated in Dutch (15-17). All subsequent mentioned questionnaires, except the RAND-36, were used at T1, T2 and T3.

HRQOL

The RAND-36 Health Survey was used at T1 to assess HRQOL (18). This instrument, which is comparable to the SF-36 (19) contains eight different subscales: physical functioning (PF), social functioning (SF), role limitations due to physical problems (RP), role limitations due to emotional problems (RE), mental health (MH), vitality (VT), bodily pain (BP) and general health perception (GH). For each subscale, scores were coded, summed up and transformed to a scale from 0 to 100, with higher scores indicating better functioning. The scores on all subscales of the RAND-36 of all study-patients were compared with a sex- and age-matched control group consisting of 232 Dutch subjects, who served to validate the Dutch version of the RAND-36 in a general population survey (18).

Pschycological well-being

Psychological distress

The General Health Questionnaire (GHQ), was used as an instrument to assess psychological distress (20). The total score gives an indication of the severity of distress; the higher the score, the more psychological distress is experienced. We made use of the 12-item version in which each item is rated on a four-point scale. Scores on the items are summed up to a total score on the scale. Baseline scores of the DTC patients were compared with GHQ scores from a Dutch general population sample (21).

Anxiety

The Hospital Anxiety and Depression Scale (HADS) (16,22) has proved to be a useful clinical indicator of anxiety and depression (23-25) among patients with somatic illnesses. We only used the seven items concerning anxiety in this study. Baseline scores of the DTC patients were compared with anxiety scores from a general population sample, taken from a survey of the general Dutch population (16).

Cancer Worries

Lerman et al. (26) developed four Likert-style items to assess breast cancer worries. These included the frequency of breast cancer worries, the impact of worries on mood, and the impact on daily functioning. In this study, these items were modified to refer to worries about thyroid cancer concerning the past 4 weeks (27). These four items were summed to create a thyroid cancer worries scale.

Statistics

The Student's t-test for independent variables and Levene's test for equality of variance was used for a comparison of scores between the study patients and the control group. Differences between the scores of Tg positive and Tg negative patients were examined with the

Mann-Whitney test. The Wilcoxon two paired sample test was applied to examine scores over time. In the Tg positive group, imaging showed recurrent disease in only 3 of 19 patients. This group was too small to analyze separately.

Results

We included 121 clinically disease free patients in long-term follow-up for DTC. After rhTSH stimulation, Tg was < 1.0 ng/ml in 101 patients (Tg – patients) and ≥ 1.0 ng/ ml in 20 patients (Tg + patients). Additional imaging was performed in 19 Tg + patients, one Tg + patient refused imaging because of pregnancy wish. Recurrence could be localized in 3 of these 19 patients.

One hundred eighteen patients (98%) returned completed questionnaires. Three patients did not return complete questionnaires (2 Tg – patients and 1 Tg + patient who did not receive additional imaging because of pregnancy wish).

Patient characteristics

The patient and disease characteristics of the two groups of patients, Tg + and Tg – patients, are shown in Table 1. No significant differences between groups were found in terms of age, age at initial diagnosis, histology of tumor, tumor stage and risk-group. The groups differed significantly in sex distribution, the Tg – group consisted of 81% females, while the Tg + group consisted of 47% females.

Table 1. Clinical characteristics at baseline

Patient and disease characteristics	All patients N=118	Tg negative patients N=99	Tg positive patients N=19	P-value Tg positive versus Tg negative patients
Age-yrs[a]	55 *(44-61)*	56 *(45-62)*	53 *(43-58)*	0.360
Sex[b]				
male	29 (25%)	19 (19%)	10 (53%)	**0.002**
female	89 (75%)	80 (81%)	9 (47%)	
Age at initial diagnosis-yrs[a]	40 *(32-51)*	40 *(32-52)*	39 *(33-50)*	0.578
Risk-group[b,c]				0.090
Low-risk	99 (84%)	85 (86%)	14 (74%)	
High-risk	12 (10%)	8 (8%)	4 (21%)	
Unknown	7 (6%)	6 (6%)	1 (5%)	
Follow-up-yrs[a]	10 (6-16)	10 (6-15)	12 (5-18)	0.426

[a] Figures are medians with inter-quartile ranges.
[b] Figures are numbers of patients with percentages in parentheses.
[c] Patients are staged at time of ablation, according to TNM classification and risk group staging (37).

Questionnaire scores

Baseline (T1)

Patients in follow-up for DTC had significantly worse scores on the RAND-36 for vitality (p=0.006) and role limitations due to physical problems (p=0.003), but a better score for role limitations due to emotional problems (p=0.014) compared to the sex- and age-matched general population control group (Table 2). Compared with the general Dutch population, no clear differences in anxiety (HADS) or psychological distress (GHQ) were found (Table 3).

At baseline, there were no differences between the two groups of DTC patients in HRQOL (Rand-36), psychological distress (GHQ), anxiety (HADS) and worries about thyroid cancer (Cancer Worries).

Table 2. RAND-36 scores of DTC patients compared with healthy control group at baseline

RAND-36 Scales[a]	DTC patients N=118	General population[b] N=232	p-value
Physical Functioning	82.1 ±21.3	78.5 ±25.3	0.2
Role-Physical	75.4 ±39.1	87.8 ±29.3	**0.003**
Bodily pain	83.7 ±22.8	80.9 ±24.6	0.32
General health	67.5 ±21.0	69.9 ±21.6	0.33
Vitality	62.7 ±19.2	68.8 ±19.2	**0.006**
Social Functioning	83.7 ±21.4	87.7 ±19.7	0.09
Role-Emotional	87.5 ±30.7	78.2 ±37.0	**0.014**
Mental Health	76.8 ±14.2	78.6 ±16.9	0.33

[a] All data are means ± SD.
[b] Sex- and age- matched control group (21).

Table 3. Psychological distress (GHQ) and anxiety (HADS) scores of DTC patients compared with healthy control group at baseline

Questionnaire[a]	DTC patients	General population	p-value
Psychological distress (GHQ)	9.9	10.2[b]	0.6
Anxiety (HADS)	4.5	3.9[c]	NA[d]

[a] All data are means.
[b] N=2425, mean age 67 years, 41% female (21).
[c] N=1901, mean age 61.3 years, 51.2% female (16).
[d] NA; not available, data for statistical comparison were not available.

T2 and T3

Tg + patients experienced increased psychological distress (p=0.04), more anxiety (p=0.03) and an increased level of cancer worries after being informed about the Tg result (T2) (p=0.04), compared with baseline. After all imaging and being informed about disease status

(T3), anxiety decreased (p=0.02). No significant change in psychological distress or cancer worries was found between T2 and T3. Additionally, no significant change in psychological distress, anxiety or cancer worries was found between T1 and T3 (figure 2A,2B,2C).

Tg – patients showed a decrease in anxiety (p=0.029) after being informed about the rhTSH stimulated Tg value (T2), anxiety level remained stable between T2 and T3, and T1 and T3. No other changes were found (figure 2A,2B,2C).

Between group comparison of Tg + and Tg- patients at T2, showed increased psychological distress (p=0.009), more anxiety (p=0.021) and more cancer worries (p=0.002) for Tg + patients. After finishing all diagnostic tests and being informed about disease status (T3), Tg + patients showed a persistent higher level of cancer worries (p=0.030) in comparison to Tg – patients (figure 2A, 2B, 2C).

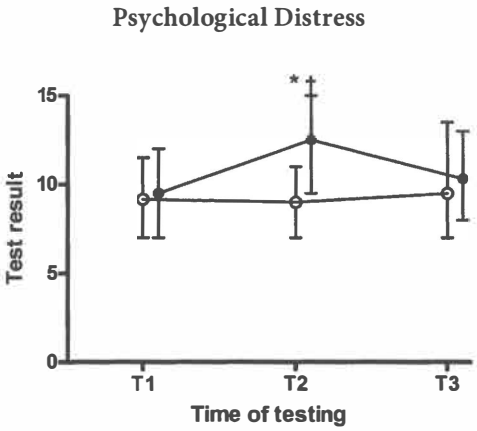

Figure 2A. *Psychological distress (GHQ) in Tg positive and Tg negative patients*

Black dots are Tg positive patients, white dots are Tg negative patients.
Median and interquartile ranges are given.
Higher scores indicate more psychological distress.
** = significant difference in test result between Tg positive and Tg negative patients.*
† = significant change in test result for Tg positive patients between T1 and T2.

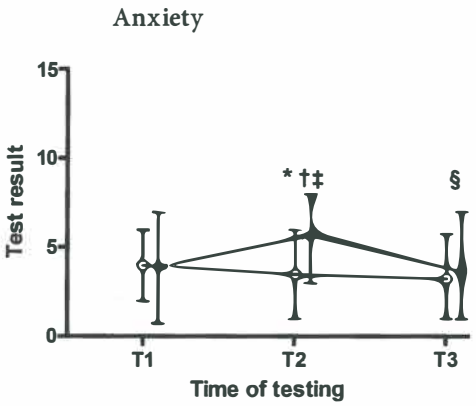

Figure 2B. *Anxiety (HADS) in Tg positive and Tg negative patients*

Black dots are Tg positive patients, white dots are Tg negative patients.
Median and interquartile ranges are given.
Higher scores indicate more anxiety.
** = significant difference in test result between Tg positive and Tg negative patients.*
† = significant change in test result for Tg positive patients between T1 and T2.
‡ = significant change in test result for Tg negative patients between T1 and T2.
§ = significant change in test result for Tg positive patients between T2 and T3.

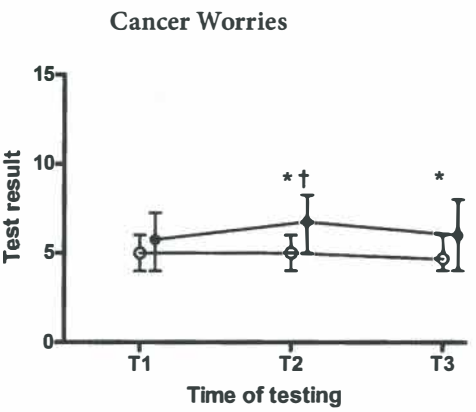

Figure 2C. *Cancer worries in Tg positive and Tg negative patients*

Black dots are Tg positive patients, white dots are Tg negative patients.
Median and interquartile ranges are given.
Higher scores indicate more worries about thyroid cancer.
** = significant difference in test result between Tg positive and Tg negative patients.*
† = significant change in test result for Tg positive patients between T1 and T2.

Discussion

In this study, we showed that clinically disease free patients in long-term follow-up for differentiated thyroid cancer (DTC) have a reduced health related quality of life (HRQOL) compared to the general population. Additionally, we showed that a positive rhTSH stimulated thyroglobulin (Tg) test in the follow-up of differentiated thyroid carcinoma has a significant negative impact on psychological health. RhTSH-Tg positive patients (Tg +) showed a temporary increase in psychological distress and anxiety compared to baseline and compared to rhTSH stimulated Tg negative (Tg -) patients. Moreover, Tg + patients showed a higher level of cancer worries (p=0.030) in comparison to Tg – patients after the Tg result, and these worries about thyroid cancer persisted despite receiving negative imaging results, compared with Tg negative patients. The majority (84%) of these Tg + patients did not have evidence of recurrent disease after diagnostic imaging.

At baseline, DTC patients showed reduced HRQOL compared with the general population, in the RAND-36. This is in line with earlier studies (5,28,29). Although included patients were clinically disease free and in long-term follow-up (median follow-up ten years), they reported lower vitality and more role limitations due to physical functioning. This implies that HRQOL remains permanently impaired after the diagnosis of differentiated thyroid cancer, despite of being cured for years. Crevenna et al. showed as well permanently impaired vitality score in the RAND-36 in patients in long-term follow-up for DTC, although longer duration of cure was associated with better scores on different quality of life items. These findings should be addressed by health care providers and patients needing additional psychological support should be recognized and supported. There were no clear differences between DTC patients and the general population in anxiety and psychological distress. A higher level of anxiety might be expected in DTC patients. After cancer treatment concerns about recurrence can persist and translate into more general forms of psychological distress such as anxiety and depression (30). Since age and gender are associated with QOL (31), the absence of a sex- and age-matched control group for these comparisons limit its interpretation.

RhTSH stimulated Tg measurement and secondly highly sensitive Tg assays are introduced in the follow-up of DTC to optimize diagnostic yield of Tg measurement. But higher sensitivity of these monitoring tests might be at the cost of specificity. Low detectable Tg values are found in patients (14) who are clinically disease free. Likewise in a significant number of patients with (low) detectable rhTSH stimulated Tg (1.0-2.0 ng/ml), no recurrence is found despite of extensive imaging (12,32). Currently, it is difficult to differentiate those in whom recurrence will be identified from others in whom Tg will spontaneously decline over time. This uncertainty can lead to unnecessary extensive diagnostic testing and considerable patient burden. Indeed, we showed that monitoring patient with rhTSH stimulated Tg measurement in the follow-up has an negative impact on psychological health for Tg + patients.

The use of rhTSH stimulated Tg measurement resulted in a considerable number of Tg + patients. After patients received this abnormal result, they indicated increased psychological distress and experienced more anxiety compared to patients with a favorable Tg negative test result. Uncertainty about the result of following, potential frightening diagnostic procedures, including radioiodine therapy, plays an important roll in this situation (7). These Tg + patients had to wait to find to out whether they still had cancer and obviously these patients also showed more worries about thyroid cancer.

Although most Tg + patients (84%) could be reassured that no cancer was found (at this moment), worries about thyroid cancer remained higher for Tg + compared to Tg – patients. These results correspond with data from studies concerning the psychological impact of false positive findings in cancer screening programs (although indeed a positive Tg test without localized recurrence is not per se a false positive finding). Abnormal screening tests for breast and cervical cancer (e.g. mammogram and Papanicolaou test) increase anxiety and distress, but these effects are generally transient (33,34). General anxiety and distress subside when findings in the end proves to be normal (35,36). However, cancer-specific concerns can prevail long-term (up to two years) after testing, although final test results are normal (33,36). These prevailing cancer worries in Tg + patients are a serious adverse psychological consequence, even more knowing that after four years follow-up in none of these patients recurrence was found.

In conclusion, we showed that patients in long-term follow-up for DTC have a reduced HRQOL. Additionally, a positive rhTSH-Tg test and the subsequent diagnostic tests induce anxiety, cancer worries and increased psychological distress, while diagnostic yield is limited. The low yield of rhTSH testing and its negative impact on QOL justifies withholding this test during long-term follow-up.

Acknowledgements

This study was funded by an effectiveness studies grant from the University Medical Center Groningen.

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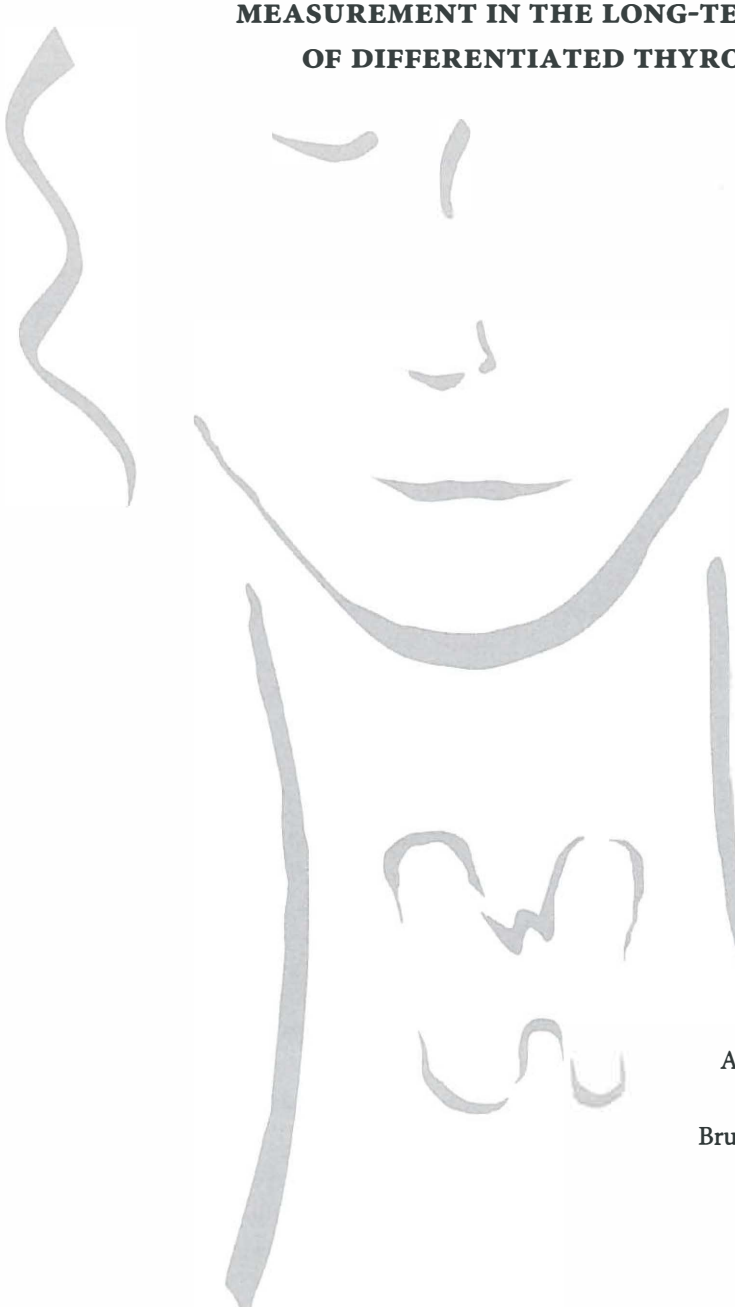
Chapter 6

Cost-effectiveness of recombinant human TSH stimulated thyroglobulin measurement in the long-term follow-up of differentiated thyroid carcinoma



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Abstract

Background: Sensitivity of thyroglobulin (Tg) measurement to detect remnants or recurrence of differentiated thyroid cancer (DTC) can be improved by measurement of Tg after stimulation with recombinant human TSH (rhTSH-Tg). We compared the cost-effectiveness of rhTSH-Tg and Tg measurement during thyroid hormone suppression therapy (Tg-on) in the long-term follow-up of DTC.
Methods and results: In 121 patients in follow-up for DTC, Tg-on and rhTSH-Tg were measured. Extensive imaging was performed in 19 patients with rhTSH-Tg ≥ 1.0 ng/ml. Only in three patients recurrence could be localized. However, two of these three patients had detectable Tg-on (≥ 0.6 ng/ml) and would have been identified without rhTSH.

Thus, rhTSH-Tg resulted in detection of one extra patient with localized recurrent disease (primary measure of effect). The cost-effectiveness ratio was €192.961, which means that an extra €192.961 had to be invested with the rhTSH protocol to detect one additional patient with localized recurrence compared to the Tg-on protocol.

When cost-effectiveness ratio was recalculated first using higher Tg cut-off values for imaging (Tg-on: 1.0 ng/ml, rhTSH-Tg 2.0 ng/ml) and second using higher Tg cut-off values in combination with only a limited imaging protocol, rhTSH-Tg resulted in respectively €160.134 and €151.226 extra costs to detect one extra patient with localized recurrence.
Conclusions: The use of rhTSH-Tg resulted in very high costs, while additional diagnostic yield compared with Tg-on was limited. This unfavourable cost-effectiveness ratio should be taken into account in the evaluation of the place of rhTSH-Tg in the follow-up of DTC.

Introduction

Thyroglobulin (Tg) measurement is the primary diagnostic test in the follow-up of patients with differentiated thyroid cancer (DTC) and is considered the most sensitive tool for detection of recurrent disease (1,2). Sensitivity of Tg measurement increases after TSH stimulation, which can be reached by thyroid hormone withdrawal or administration of recombinant human TSH (rhTSH).

Thyroid hormone withdrawal induces clinical hypothyroidism which will lead to a considerable quality of life impairment (3). Besides, thyroid hormone withdrawal has a substantial economic impact. A Dutch study (4) showed a mean of 59% lost time at work during the withdrawal period, costing an estimated amount of €2.495.791 per year in the Netherlands (calculated on the basis of 450 patients).

RhTSH administration is an alternative approach for preparing patients for serum Tg measurement. It is a relatively expensive adjuvant for testing (€1062 excluding the cost of injecting the drug) but avoids hypothyroidism and the associated impairment of quality of

life (3,5), while it is effective in stimulating Tg production (5,6). Therefore, rhTSH has been widely introduced in the clinical routine and has now a prominent place in the follow-up of low-risk patients to check for the completeness of thyroidectomy and I-131 remnant ablation (7-9).

Although rhTSH may have a place in the early follow-up, the value of measurement of rhTSH stimulated Tg (rhTSH-Tg) in the long-term follow-up (> 1 year after initial treatment) of DTC is unknown. Data about the additional diagnostic yield of rhTSH-Tg compared with Tg measurement during thyroid hormone therapy (Tg-on) without TSH stimulation are lacking. We evaluated in a prospective study the diagnostic yield of rhTSH-Tg in the detection of recurrences in clinically disease-free patients in long-term follow-up for DTC (10). We observed that rhTSH-Tg had very limited additional diagnostic yield compared with Tg-on measurement with a sensitive Tg assay.

Since follow-up of DTC is lifelong and the prevalence of thyroid cancer worldwide is 475.200 (11), considerable medical costs are generated. The extensiveness of the follow-up regimen and the used diagnostic procedures will largely influence these medical costs. As health care systems are limited in their financial resources, assessing the balance between costs and effects of a new diagnostic procedure as rhTSH stimulated Tg measurement is crucial for medical decision making.

Unfortunately, data about cost-effectiveness of follow-up protocols in DTC are lacking. For this reason, as part of the prospective study, we determined and compared the cost and effects of rhTSH-Tg with Tg-on measurement in clinically disease free patients in long-term follow-up for DTC.

Methods

Design of the study

This prospective study evaluated the diagnostic yield of rhTSH-Tg in the detection of recurrent disease compared with Tg-on measurement in clinically disease free patients in long-term follow-up for DTC. The study protocol and main findings of the rhTSH study have been reported in detail elsewhere (10).

In brief, patients with DTC who were clinically disease free for > 1 year were included. Clinically disease free was defined as no clinical evidence of recurrent or persistent DTC and undetectable Tg-on for at least 1 year. During routine follow-up in our outpatient-clinic, Tg was measured with an immunoradiometric assay (Cis Bio International) with a functional sensitivity of 1.5 ng/ml. However, in the study, all Tg measurements were performed with a more sensitive Tg assay (Nichols Advantage® Tg assay, Nichols Institute Diagnostics, San Clement, CA, USA) with a functional sensitivity of 0.6 ng/ml (12).

On the basis of Tg result after rhTSH, patients were divided into two groups. Patients with rhTSH-Tg < 1.0 ng/ml received no further testing. Patients with rhTSH-Tg ≥ 1.0 ng/ml underwent imaging procedures in order to attempt to localize any possible recurrence. In all these patients 18-F Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET), ultrasound (US) examination of the neck (with fine needle aspiration when indicated) and a posttherapy I-131 whole body scan (WBS) after treatment with 150 mCurie I-131 was performed. Additional imaging was performed on indication. An expert panel assessed disease status on the basis of all performed imaging and categorised patients as no recurrence localized or recurrence localized. In addition, therapeutic consequences of these results were determined.

A total of 121 Tg-antibody negative, clinically disease free patients were included. All patients had undergone (near) total thyroidectomy followed by radioiodine ablation, and used a suppressive dose of levothyroxin.

Economic evaluation

The aim of the economic evaluation was to assess the cost-effectiveness of rhTSH-Tg compared with Tg-on measurement. The primary measure of effect in this economic evaluation was the number of patients with localized recurrence, detected in the diagnostic tests. The costs analysis was performed from a healthcare perspective, where only costs made for the benefit of diagnosis were taken into account. The time horizon of the economic evaluation varied between patients. Starting point for all patients was the moment the diagnostic cycle started by performing Tg-on measurement (Figure 1). Endpoint was the moment Tg-on was < 1.0 ng/ml or in case Tg was ≥ 1.0 ng/ml the moment that additional diagnostic testing was completed. Since the primary measure of effect was the number of patients with localized recurrence, costs for treatment of recurrent disease were not included in the analysis.

In the economic evaluation, the price level of 2006 was used. Costs of outpatient visits and general practitioners visits were valued based on Dutch standard prices (13). Information on costs of medication was obtained from the Dutch Health Care Insurance Board (CVZ) (14). Laboratory tests and diagnostic imaging were valued according to tariffs of the National Health Tariffs Authority (CTG/ZAio) (15). For admission to an isolation room and an additional post therapy scan no standard prices were available. For these cost categories the costs were based on true resources used and time invested by staff and were calculated in one of our previous studies (16). These costs were used after indexing to the price level of 2006. Since the time horizon was shorter than one year in all patients, costs and effects were not discounted.

All patients were tested following two procedures: Tg-on and rhTSH-Tg. For the economic evaluation these two procedures were considered separate as two scenarios to assess the costs of both follow-up strategies. In the first scenario, costs and effects of the Tg-on measurement and subsequent imaging were established. Costs of the Tg-on measurement

were based on true resources used in the total group of 121 patients. Costs of imaging were based on the average use of imaging techniques in the group of patients with a detectable Tg (≥ 0.6 ng/ml) based on Tg-on measurement. In the second scenario, costs and effects of imaging were based on the average use of imaging techniques in the group of patients with rhTSH-Tg ≥ 1.0 ng/ml (n=19).

To adjust for possible changes in the future in the Tg cut-off value for additional imaging, we compared costs and effects when Tg-on ≥ 1.0 ng/ml and rhTSH-Tg ≥ 2.0 ng/ml were used as cut-off levels. Additionally, we calculated costs and effects when using a limited imaging protocol for localizing recurrent disease, consisting of only neck ultrasound and a posttherapy I-131 WBS after treatment with 150 mCurie I-131. In this limited scenario, FDG-PET and additional anatomic imaging (MRI, CT) were omitted.

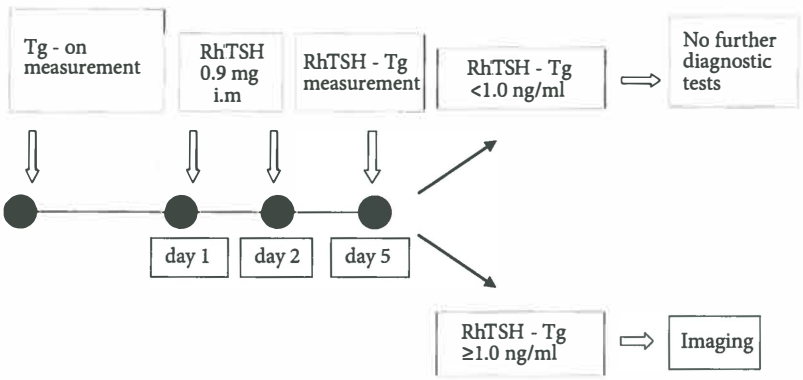

Figure 1. *Study design*

Results

The results of this clinical study have been published in detail elsewhere (10).

Clinical characteristics of the study-population are presented in Table 1. At baseline, Tg-on was detectable (≥ 0.6 ng/ml) in 6 of the 121 patients. RhTSH-Tg was ≥ 1.0 ng/ml in 20 patients (17%). In 5 of these 20 patients, Tg-on had also been detectable (≥ 0.6 ng/ml). In one patient Tg-on was detectable but rhTSH-Tg was < 1.0 ng/ml. No imaging was performed in this patient, because indication for imaging was based on the rhTSH-Tg result. Further calculations are based on these 5 patients with Tg-on ≥ 0.6 ng/ml.

Imaging was performed in 19 of the 20 eligible patients (one patient refused imaging because of pregnancy wish). After evaluation of all images, 16 patients showed no localization of a recurrence and 3 patients were classified as having recurrent disease. Two of these three patients with localized recurrent disease had detectable Tg-on, meaning that these patients would have been identified without the procedure of rhTSH stimulation.

After 4 years follow-up, none of the 16 Tg positive patients with negative imaging showed recurrent disease. Additionally, in the Tg positive patient who refused imaging because of pregnancy wish no recurrence has been found.

Table 1. **Clinical characteristics at baseline**

Characteristic	All patients n=121
Sex- no. (%)	
Female	92 (76%)
Male	29 (24%)
Age[a] (years)	54 (20-73)
Histology- no. (%)	
Papillary	86 (71%)
Follicular	29 (24%)
Hürthle cell	6 (5%)
Follow-up[a] (years)	10 (1-34)
TNM-classification[b] – no. (%)	
T1-T3	100 (82%)
T4	3 (3%)
Tx	18 (15%)
N0	85 (70%)
N1	32 (27%)
Nx	4 (3%)
M0	120 (99%)
M1	1 (1%)

[a] Data are given as number (percentage) or median with range.
[b] TNM-classification (34)

Economic evaluation and costs

Costs of Tg measurement procedure

The mean total costs per patient were €129 for Tg-on measurement in itself and €1232 for rhTSH-Tg in itself (Table 2). The use of rhTSH, generated €1103 (€1232-€129) extra costs per patient. These higher costs mainly resulted from the costs of the rhTSH injection (€1062).

Table 2. Costs of initial diagnostics per patient

Cost category	Tg-on protocol (n=121) Costs (€)	RhTSH-Tg protocol (n=121) Costs (€)
Out patient visits	103	103
Laboratory tests	26	26
Medication (rhTSH injections)	–	1062
General Practitioner	–	41
Total	**129**	**1232**

Table 3. Mean costs of additional diagnostic tests per patient

Cost category	Tg-on protocol (n=5) Costs (€)	rhTSH protocol (n=19) Costs (€)
Diagnostic imaging	2168	1724
Stay in isolation room	2438	2438
Outpatient visits	184	230
Total	**4790**	**4392**

Costs and effects of additional imaging

Additional imaging was performed in 5 patients according to the Tg-on protocol (Tg-on ≥ 0.6 ng/ml) and in 19 patients according to the rhTSH protocol (rhTSH-Tg ≥ 1.0 ng/ml). Mean total costs per patient for imaging procedures were €4790 in the Tg-on protocol and €4392 in the rhTSH protocol (Table 3). The Tg-on protocol resulted in the detection of two patients with localized recurrence, rhTSH-Tg resulted in the detection of three patients with localized recurrence. Costs per patient with localized recurrent disease were €19780 in the Tg-on protocol and €77.507 in the rhTSH protocol, so the rhTSH protocol generated €57.727 extra costs per patient with localized recurrence (Figure 2, 3). This difference in costs was predominantly caused by the higher number of patients referred for imaging in the rhTSH protocol (19 patients versus 5 patients in the conventional protocol). Imaging in these 14 extra patients resulted in one additional patient with localized recurrent disease.

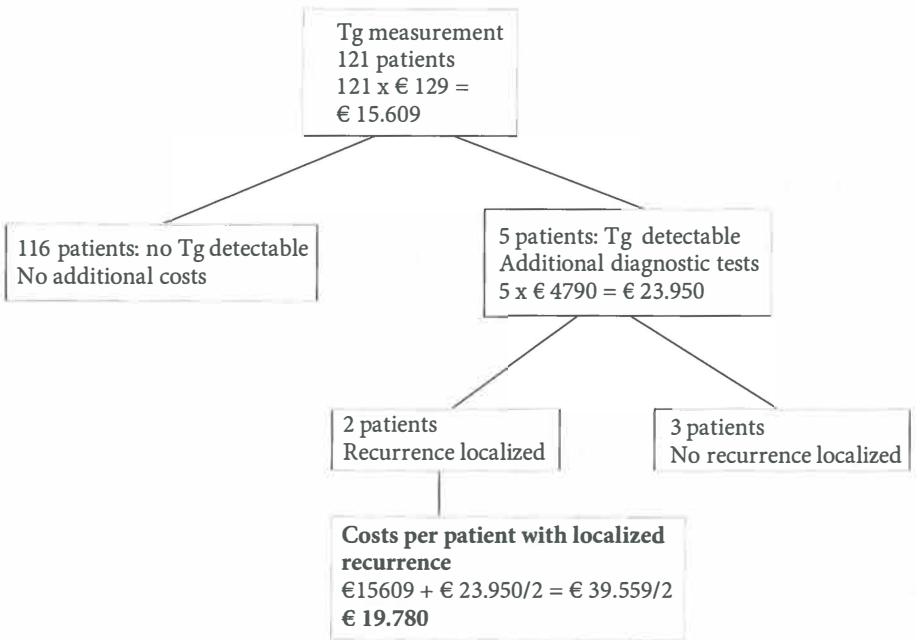

Figure 2. *Costs and effects of the Tg-on protocol (Tg cut-off 0.6 ng/ml)*

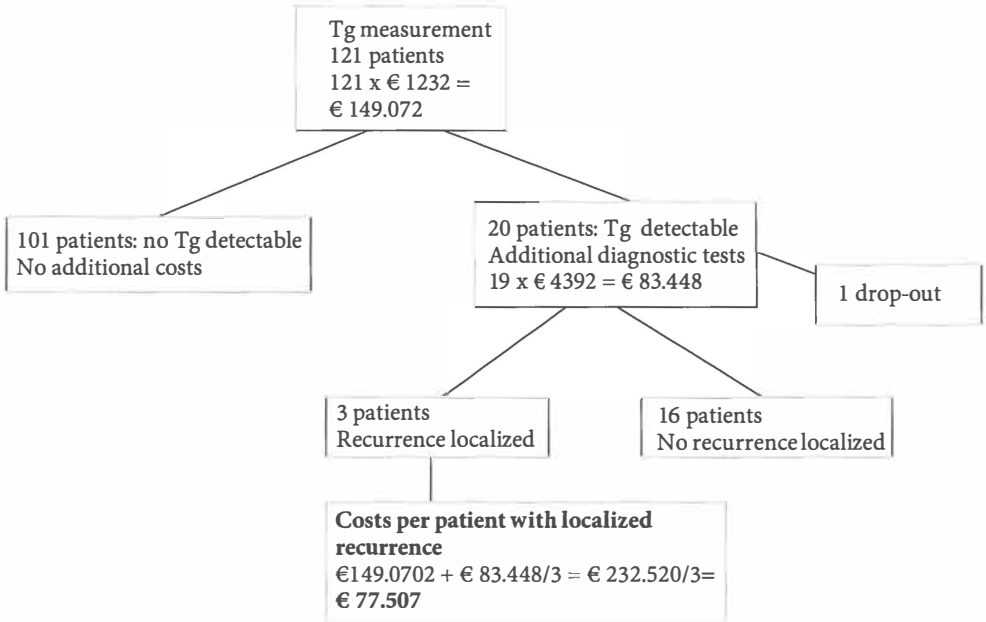

Figure 3. *Costs and effects of the rhTSH protocol (Tg cut-off 1.0 ng/ml)*

Cost-effectiveness ratio

The cost-effectiveness ratio (Δ costs/ Δ effect) was €192.961 (€232.520 – €39.559 / 1), meaning an extra 192.961 euros have to be invested with the rhTSH protocol to detect one additional patient with localized recurrent disease compared to the Tg-on protocol.

Cost and effects of two scenarios with higher Tg cut-off value

When Tg-on cut-off value was increased to 1.0 ng/ml, three patients were eligible for additional diagnostic testing. This protocol would result in the detection of two patients with localized recurrence and costs per patient with localized recurrence would be €16.044 (Table 4). One patient with disease activity would be missed, who would have been identified with the rhTSH protocol. This patient was also missed in the Tg-on protocol when using Tg ≥ 0.6 ng/ml as cut-off (detection limit of the assay). The cost-effectiveness ratio, comparing with the rhTSH protocol (cut-off 1.0 ng/ml), was €200.432 (€232.520 – €32.088 / 1) (Table 4).

When rhTSH stimulated Tg cut-off value was increased to 2.0 ng/ml, 10 patients were eligible for additional diagnostic testing. Yet all three patients with localized recurrence would have been detected and costs per patient with localized recurrence would be €64.074. The use of rhTSH resulted in €160.134 extra costs (cost-effectiveness ratio: €192.222 – €32.088 / 1) to detect one extra patient with recurrent disease, comparing this rhTSH protocol (cut-off 2.0 ng/ml) with the Tg-on protocol with the adjusted cut-off level of 1.0 ng/ml (Table 4).

Cost and effects of two scenarios with higher Tg cut-off value and limited imaging protocol
The limited imaging protocol consisted of US examination of the neck and a posttherapy I-131 WBS. Using the higher Tg cut-off values for additional imaging (Tg-on: 1.0 ng/ml and RhTSH-Tg: 2.0 ng/ml) in combination with this limited imaging protocol would result in the identification of two recurrences in the Tg-on protocol and three recurrences in the rhTSH-Tg protocol. Mean total costs per patient for imaging procedures were €3159 in the Tg-on protocol and €2724 in the rhTSH protocol. Costs per patient with localized recurrent disease were €12.543 in the Tg-on protocol and €58.771 in the rhTSH protocol. An extra €151.226 have to be invested with this adjusted rhTSH protocol to detect one additional patient with localized recurrent disease compared to the Tg-on protocol (Table 4).

Table 4. Costs and effects of different protocols

	Tg-on protocol (0.6 ng/ml)	RhTSH protocol (1.0 ng/ml)	Tg-on protocol (1.0 ng/ml)	RhTSH protocol (2.0 ng/ml)	Tg-on protocol (1.0 ng/ml) *Limited imaging protocol*	RhTSH protocol (2.0 ng/ml) *Limited imaging protocol*
Tg detectable above cut-off value and additional imaging performed[a]	5	19	3	10	5	19
Recurrence localized[b]	2	3	2	3	2	3
Costs per patient with localized recurrence	€19.780	€77.507	€16.044	€64.074	€12.543	€58.771
Cost-effectiveness ratio[c]		€192.961 *Compared to Tg-on (0.6 ng/ml)*		€160.134 *Compared to Tg-on (1.0 ng/ml)*		€151.226 *Compared to Tg-on (1.0 ng/ml) with limited imaging protocol*

[a] Number of patients with Tg above cut-off level who were referred for additional imaging.
[b] Number of patients with localized recurrent disease.
[c] Extra cost for the detection of one additional patient with localized recurrence.

Discussion

The use of rhTSH stimulated Tg measurement in the long-term follow-up of 121 DTC patients resulted in the detection of one extra patient with localized recurrent disease compared to Tg measurement during thyroid hormone suppression therapy with a sensitive Tg assay, at the cost of an extra 192.961 euros. We highly doubt if these extra costs are worth the additional effect.

The higher costs for the rhTSH stimulated Tg procedure were firstly due to the expensive rhTSH injections in itself and secondly due to the large amount of additional diagnostic procedures required. In 101 patients with rhTSH-Tg < 1.0 ng/ml, the comprehensive procedure of Tg measurement with rhTSH injections cost €1103 extra per patient while it only confirmed the absence of disease (demonstrated by the Tg-on protocol). Additionally, with the use of rhTSH 14 extra patients were suspected of recurrent disease and subsequently underwent highly costly additional testing, including I-131 WBS after high dose radioiodine treatment. Imaging was negative in 13 of these 14 extra patients and unnecessary. Consequently, the positive predictive value (PPV) of this rhTSH-Tg was very low (3 out of 19 patients recurrence localized, PPV 16%). Besides extra costs, imaging caused substantial patient burden in terms of concerns about possible recurrence of cancer and extra hospital visits including unnecessary radioiodine treatment. In our opinion, the potential reassurance and relief of negative imaging do not outweigh this patient burden.

The clinical significance of elevated rhTSH-Tg values in patients in whom no tumour could be identified is insecure. In this study, in none of these patients recurrence was found during 4 years follow-up. Either tumour recurrence or a spontaneous decline in Tg can occur over time, but distinguishing these patients is difficult (17-19). An increase in serially determined Tg levels is more informative than the absolute value of Tg in the lower range (12,18-20). Extensive imaging only when Tg rises above a certain cut-off level will largely contribute to cost-effective follow-up management. Additionally, with the introduction of highly sensitive Tg assays this Tg measurement can be performed during thyroid hormone suppression therapy (10,21-23), saving the costs of rhTSH stimulation.

We included patients irrespective of prognostic factors influencing risk of recurrence and follow-up duration. Although the presence of the established risk factors result in a reduced life expectancy (24), also initial low-risk patients can die from thyroid cancer (25), illustrating that distinction between high and low-risk is not perfect (26). In the present study, recurrent disease was found in two low-risk patients (follow-up 5 and 12 years) and one high-risk patient (follow-up 16 years), once again demonstrating the limitation of the current staging systems (10). Moreover, this study-population reflects the variety of patients in follow-up for DTC in daily clinical practice and results of are applicable to all patients in follow-up for DTC.

Future changes in either the Tg-on or the rhTSH protocol might influence its cost-effectiveness. In the present study we chose rather stringent Tg cut-off values, influencing the number of patients referred for imaging. No consensus exists about the optimal threshold for additional imaging, but most authors consider a stimulated Tg > 2.0 ng/ml indicative for recurrent disease (27). However, the large between-method variability in Tg assays that persists despite CRM-457 standardization can lead to difficulties with comparison of Tg results of different assays (28). Additionally, Tg cut-off levels will continue to evolve as new Tg assays are introduced (29). In this study, when using adjusted Tg-on cut-off value of 1.0 ng/ml and rhTSH-Tg cut-off value of 2.0 ng/ml, unnecessary imaging was prevented in respectively two and nine patients, saving costs without influencing effectiveness. Despite of these adjustments, rhTSH-Tg still resulted in €160.134 extra costs to detect one extra patient with localized recurrence.

Indeed, the extensive imaging performed in the rhTSH study also influenced the cost-effectiveness. Firstly, in this study FDG-PET was performed in all patients with detectable Tg. Currently, in most clinics FDG-PET is not a first-line tool in Tg positive patients and is only used in selected cases, mostly when I-131 WBS is negative (27,30,31). Secondly, we used in some cases anatomic imaging (MRI, CT) for optimal differentiation between normal and pathologic imaging and treatment planning. These techniques were not essential for the primary goal, the *localization* of recurrence. We composed a limited imaging protocol including neck ultrasound and posttherapy WBS, which is the standard of care in most hospitals when patients have detectable Tg in follow-up. Using these techniques, in combination with the adjusted Tg cut-off value (2.0 ng/ml), all recurrences were identified, but still an extra €151.226 had to be invested to detect one additional patient with localized recurrence compared with Tg-on measurement. These adjusted Tg cut-off levels and limited imaging scenarios only marginally influenced the cost-effectiveness ratio and confirmed the high costs of the use of rhTSH stimulation.

Other studies analysing the cost-effectiveness of Tg-on and rhTSH-Tg in the follow-up of DTC are lacking. Only one abstract reported a cost-utility analysis of four strategies of follow-up in thyroid cancer, combining a method of stimulation (rhTSH or thyroid hormone withdrawal) and a testing protocol (neck ultrasound + Tg + WBS or neck ultrasound + Tg alone) (32). The combination of rhTSH-Tg and neck ultrasound was the most cost-effective strategy. However, a strategy with Tg-on measurement was missing in this analysis. Therefore, the results of this present study are an important contribution in the evaluation of rhTSH-Tg and Tg-on in the long-term follow-up of DTC, even more since the need for (rh) TSH stimulation in this phase is nowadays more and more challenged (22,23).

The costs of rhTSH stimulated Tg are extremely high, also when cut-off levels are adjusted and limited imaging modalities are used, and in our opinion do not outweigh the benefit of the detection of one extra patient with localized recurrence. Moreover, regular serial Tg-on measurement with a sensitive Tg assay anyhow would have identified this single

patient, since the change in Tg over time is more informative than a single Tg determination (20). Tg-on will increase during serial Tg-on measurement when recurrent disease is actually present. Moreover, differentiated thyroid cancer is a relatively benign disease with generally a slow course. There is no evidence to support that earlier intervention in this patient ultimately will affect mortality (33).

In conclusion, our study compared costs and effects of Tg-on and rhTSH-Tg in the long-term follow-up of patients with differentiated thyroid cancer. RhTSH-Tg had a limited additional clinical benefit in these patients but costs per detected patient with evidence of disease were excessively high. This unfavourable cost-effectiveness ratio should be taken into account in the evaluation of the place of rhTSH-Tg in the follow-up of DTC.

Acknowledgements

This study was funded by an effectiveness studies grant from the University Medical Center Groningen.

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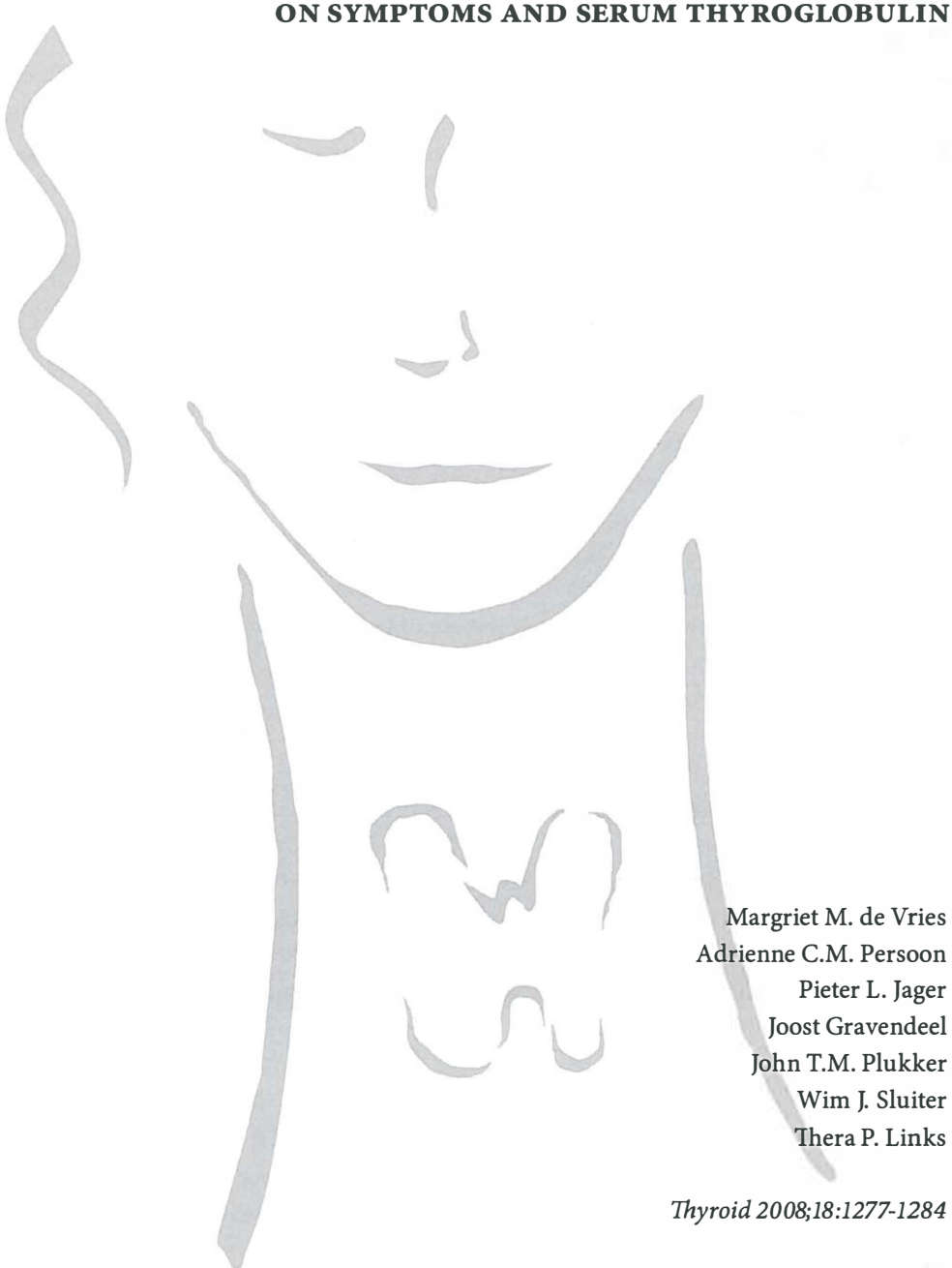
Chapter 7

Embolization therapy of bone metastases from differentiated thyroid carcinoma: effect on symptoms and serum thyroglobulin



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Thyroid 2008;18:1277-1284

Abstract

Background: Selective embolization therapy (SET) has been employed to treat a number of malignant tumors, but experience with its use in metastatic differentiated thyroid carcinoma (DTC) is limited. Here we report our experience with the effect of SET on symptoms and serum thyroglobulin (Tg) in patients with bone metastases from DTC.
Methods: This was a retrospective study of 13 patients with bone metastases from DTC who underwent 65 embolizations for bone metastases in 43 sessions. In the treated patients, symptoms considered related to bone metastases were compared before and about 4-7 weeks after the embolization session. Embolization sessions were excluded for analysis if concomitant therapy had taken place within 4-7 weeks before and/or after the session. Serum Tg concentrations were employed as an index of tumor debulking by SET. We attempted to estimate the influence of SET on survival time in patients with disseminated DTC who did, and an historical control group of patients with disseminated DTC who did not received SET.
Results: After exclusion of 12 (of which 3 sessions failed) out of 43 sessions, clinical symptoms such as pain and neurological symptoms decreased after 17, increased after 6 and did not change after 8 procedures. In 43 sessions, 20 of which were excluded (including the 3 sessions that failed), serum Tg decreased after 14 and increased after 9. The median standardized survival time of the group that received embolization was not significantly different to that of the group that did not receive embolization.
Conclusions: Embolization therapy does not appear to improve life expectancy, but in selected patients can achieve palliation of pain, prevent neurological damage, can reduce tumor burden and give devascularization of the tumor before surgery.

Introduction

Although overall survival in patients with differentiated thyroid carcinoma (DTC) is excellent, patients with persistent disease have a life expectancy of approximately 60% of the normal residual life span (1). The challenge in treating this persistent disease is to improve survival and control symptoms such as pain and different neurological symptoms. Standard treatment consists of thyroidectomy followed by high-dose radioiodine and lifelong thyroid hormone suppression therapy. In cases of persistent disease, surgery and occasionally additional external beam therapy, are used. Other treatments, including labeled octreotide, have limited results (2).

Selective embolization therapy (SET) for the treatment of bone tumors was first described by Feldman et al. in 1975 (3). Camille *et al.* (4) were the first to write about pre-operative embolization therapy for thyroid carcinoma. They wrote about embolization of metastases from thyroid carcinoma before surgery in four cases with spinal or pelvic metastases.

Several case reports with embolization therapy in the treatment of thyroid cancer are described (5-10). Few reports, including one report written by our group, deal with embolization therapy for bone metastasis in thyroid cancer (11,12); others concern direct embolization of the primary thyroid tumor (13,14) or the use of embolization as a preoperative procedure (15-18). These reports indicated that some patients achieved a rapid reduction in pain and tumor burden. Barton et al. (19) showed that embolization is generally an effective treatment for bone metastases of different primary tumors. It is known that embolization therapy together with antivascular therapy (Marimastat) has no additional effect for clinical symptoms (20). Previous studies have shown that clinical improvement was not always concordant with tumor regression on imaging (12).

We report our experience with the effect of SET on symptoms and serum thyroglobulin (Tg) in patients with bone metastasis from DTC, and we investigate if SET has an additional value to life expectancy.

Materials and Methods

The University Medical Center Groningen is the major referral center in the northern part of The Netherlands for treatment of patients with DTC. The treatment regimen and follow-up were described earlier (21) and consisted of a total thyroidectomy and I-131 therapy, with Tg measurement under thyroxine suppression therapy after a negative posttherapeutic whole-body scan (WBS).

The patient group consisted of 13 patients with disseminated DTC who received SET for their bone metastases to control pain, and/or to achieve tumor debulking, and in specific cases to obtain devascularization before surgery. An additional nonrandomized group of 87 patients with disseminated DTC who did not receive SET (No-SET group) was used to estimate the impact of SET on survival. Between 1996 and 2006 the 13 SET-treated patients underwent 65 embolizations in 43 sessions. Eleven of these patients had persistent disease after initial therapy, nine of them presented with only bone metastases. The other two patients were in remission after initial treatment, but developed recurrent persistent disease with bone metastases. The SET procedures were executed after obtaining informed consent.

The 87 patients in the No-SET group were part of the large cohort that has been described earlier(1). Sixty seven of these patients had persistent disease after their initial surgical and radioiodine treatment, and 20 patients developed recurrent disease after this initial treatment and did not have a second remission after the additional treatment.

Regarding terminology, an embolization session refers to several embolizations in one patient on the same day, and an embolization refers to as one embolization procedure.

The success of embolization was evaluated by additional angiography after the embolization session. After 3-4 months the success of the embolization was measured by mag-

netic resonance imaging and computed tomography. Embolizations that were at least 60% complete were considered partially successful, and embolizations that were 100% complete were considered completely successful.

Completely and partially successful embolizations were included in the analysis unless there was concomitant therapy near the time of the procedure. In 43 embolization sessions during which 65 embolizations were administered, 48 embolizations were successful, 13 embolizations were partially successful and 4 embolizations were not successful. To evaluate the effect of therapy (symptoms and Tg levels), no concomitant therapies in a period of 4-7 weeks before and after the embolization sessions were accepted for evaluation. Therefore, nine embolization sessions were excluded because of concomitant surgery (four sessions and four embolizations), antivascular therapy (three sessions and eight embolizations), and I-131 therapy (two sessions and two embolizations). In eight other embolization sessions no Tg levels were available. Of the total 12 and 20 embolization sessions that were excluded, both contained the 4 embolizations executed in 3 sessions that failed. In sum, 23 embolization sessions were evaluable for Tg levels and 31 sessions for symptoms.

Persistent disease after initial therapy was defined as clinical evidence of thyroid cancer found at any visit after ablation. Recurrent disease was defined as tumor recurrence indicated by newly detectable Tg during suppression therapy or clinical evidence of disease detected by other technique. The characteristics of the SET and non-SET groups are given in Table 1. Both groups were compared for differences in survival. Most of the patients in the embolization group have follicular thyroid carcinoma and M1 tumors. For survival, both subgroups of patients were also compared separately with the same subgroup in the control group.

Table 1. **Patient characteristics**

	Embolization group	Control group	P-value
Sex: male/female	2/11	34/53	0.20
Age (± SD)	57.5 (14.1)	60.7 (15.7)	0.29
TNM classification			
N0/N1	13/0	44/43	0.005
M1/M0	11/2	23/64	0.0005
Histology (pap/foll/Hürthle)	0/12/1	43/30/14	0.0003

Pap, papillar; foll, follicular; Hürthle, Hürthle cell carcinoma (patient number 10)

Laboratory methods

Serum Tg was measured by a commercially available radioimmunoassay (Cis Bio International, Gif-sur-Yvette, France), with a lower detection limit of 1.5 ng/mL. In cases of an undetectable serum Tg, the presence of Tg antibodies was evaluated by recovery of added standard Tg. Tg antibodies were considered to be absent if recovery was > 85%. None of our patients had Tg antibodies.

After March 2004 an immunochemiluminometric Tg assay was introduced (Nichols Advantage® Tg assay; Nichols Institute Diagnostics, San Clemente, CA), detection limit < 0.6 ng/ml. For Tg antibody detection the Nichols Advantage ® TgAb assay (Nichols Institute Diagnostics) with a cut-off value for TgAb positivity of 2 mIU/L was introduced (22).

Embolization technique

Before embolization, all the tumor-supplying vessels were visualized by diagnostic angiography. Embolization was performed during the same session. A no. 6 French (F) sheath was placed into the femoral artery, to facilitate catheter exchange. Then a 6 F guiding catheter (Boston Scientific, Natick, MA) was inserted proximal in the main tumor-feeding artery. With a microcatheter (Excel 14;Boston Scientific) a superselective microcatheterization of the tumor vessels was performed. The tumor was embolized with repetitive small injections of polyvinyl alcohol foam particles of 150-250 microns (Contour emboli, Target Therapeutics, Fremont, NE). The treated site of the metastases and the embolized arteries are shown in Table 2. With additional angiography, the direct result of the embolization session was documented. For the detection of side-effects, including the postembolization syndrome as flu-like symptoms or fever (11) and technical complications, all patients in whom embolization was performed were clinically observed during 24-48 hours.

Effect of therapy

The effect of the therapy was evaluated by clinical complaints such as pain, mobility, insensibility, and Tg levels. These data were collected from the patient charts retrospectively.

Clinical complaints of the local metastases were categorized as regression, stabilization, or progression. The clinical complaints before the embolization session were compared with those about 4-7 weeks after the embolization session.

Tg was measured 3 weeks before (range, 0-136 days) and up to 7 weeks (range, 10-164 days) after embolization during thyroid stimulating hormone (TSH) suppression. The individual standardized survival time was calculated as the ratio between the observed survival time of an individual and the median residual life span of the individuals with the same age in the general population in the year of diagnosis as described earlier (1).

Statistical analysis

Differences in standardized survival were analyzed by log rank test. Continuous variables are given as mean with SD; differences were tested by Mann-Whitney U-test. Differences in prevalences were tested by chi-square test. Changes in subjective complaints and Tg concentrations were tested by sign-test. P-values less than 0.05 were considered significant.

Results

Table 1 shows the characteristics of the SET and No-SET groups. More females were present in the embolization group, but age was comparable in both groups. The prevalence of distant metastases at diagnosis was significantly higher in the SET group ($p < 0.0005$) than in the No-SET group, and positive regional nodes were not present at diagnosis ($p < 0.005$). There were significantly more ($p < 0.0003$) follicular thyroid carcinomas in the SET group than in the No-SET group. Twelve patients in the SET group had follicular thyroid carcinoma, one patient (no.10) had Hürthle cell carcinoma.

Table 3 shows the characteristics of individual patients, the number of embolizations, their locations and additional therapies. Eight patients in the SET group were locally treated with external beam therapy; five of these patients had this therapy before the embolization session. The mean time of external beam therapy before an embolization session was 10.5 months with a range of 1.5-20.5 months. Of the 13 embolizations that partially succeeded and the four embolizations that failed, external beam therapy was not given before embolization.

Figure 1 shows the angiogram made before the embolization session. In Figure 2A and Figure 2B the situation before and after embolization of the left side is visible after finishing the right side of L3. Indications for embolization were tumor debulking before I-131 therapy (42.5%), preventing neurological damage (35%), diminishing complaints of pain (45%) and embolization before debulking surgery (10%). In total the percentages are more than 100% because some embolization procedures had more indications.

Table 2. Arteries treated with embolization therapy

Site metastases[a]	Embolized artery
Patient 1	**Embolized artery**
1. acetabulum(r)/os ischii/ ramus superius ossis pubis	internal iliac a.(r)
2. os ischium(r)/ramus ossis pubis(r)	internal iliac a.(r) tumor branches/medial circumflex of femoral a.(r)
3. acetabulum(r)	not specifically mentioned
4. relapse proximal and at the same height of known pelvis metastase(r) os ischium extended to medial backside of acetabulum and os pubis(r)	internal iliac a.(r) (tumor branches)
5. os ischii(r)/sacrum/acetabulum(r)/os pubis	medial and lateral circumflex of femoral a.
6. os ilium medial/sacrum/os ischii/upper part medial os pubis(r)	internal iliac a.(r)
7. os ilium lateral	gluteus maximus a.(r)
8. ramus ossis pubis superior and inferior(l)	internal iliac a.(l) (tumor branches)/tumor branch from retroperitoneal a. from external iliac a.(l)
9. pubis ring	separate branches from profunda femoris a.
10. os ileum(r)	separate branches from profunda femoris a.
11. os pubis(l)	separate branches from profunda femoris a.
Patient 2	**Embolized artery**
1. L4(r)	lumbar spinal a. L3(r) and L4(r,l)
2. L4(l)	lumbar spinal a. L3(l,r) (collateral a.) (right side by means of microcoil)
3. L4	lumbar spinal a.(r) (collateral a.)
Patient 3	**Embolized artery**
1. humerus proximal(l)	lateral upper arm a. (tumor branches incl. coiling and separate branch)
2. os ilium lateral (r)	internal iliac a.(r) (3 main branches)
3. humerus proximal (l)	axillaris a.(l) (tumor branches)
4. os ilium(r)	internal iliac a.(r) (tumor branches)
Patient 4	**Embolized artery**
1. 6th rib(l)	costal a. 6 and 7(l) (including coiling)
Patient 5	**Embolized artery**
1. Th6, Th7(r)	costal a. 7(r) (including coiling)
2. Th6, Th7(r)	costal a. 6 and 8(r) (tumor branches)
3. scapula	costal a. 6 and 8 (r) (tumor branches)
4. Th6, Th7(r)	costal a. 7(r) (including microcoil)
5. Th6, Th7(r)	costal a. 7(r) (including microcoil)
6. pelvis/sacrum(l)	lumbar spinal a.(l)
7. Th5(r)	intercostal a. Th6(r)
Patient 6	**Embolized artery**
1. L3, L4(l)	lumbar spinal a. L3(l) and L4(l)
2. L3, L4(l)	lumbar spinal a. L4(l,r)(proximal branch)
3. L3, L4(l)	lumbar spinal a. L3(r) (tumor branches)

Patient 7	Embolized artery
1. os ilium(r) with infiltration in sacrum(r), underpart L5 lateral, acetabulum, os ischi	internal iliac a.(r)/gluteal a. with collaterals to circumflex of femoral a. and the lowest lumbal a.(r)
2. pelvis(r)	internal iliac a.(r)(including microcoil)/circumflex of femoral a. (tumor branches)
3. pelvis(r)	internal iliac a.(r) (3 branches including coiling)
4. pelvis(r)	internal iliac a.(r) (collateral tumor branches including microcoil)
5. pelvis(r)	lateral circumflex of femoral a.(tumorbranches)/ internal iliac a.(r) (tumor branches)
6. pelvis(r)	internal iliac a.(r)
7. os ilium lateral(r)	internal iliac a.(r)
8. sacrum medial(r)	internal iliac a.(r)
9. os pubis medial/cranial(r)	internal iliac a.(r)
10. os ilium(l)	internal iliac a.(l)
11. os ilium(r) medial/cranial	lumbar spinal a. L4(r)
12. ilical(l) and at the SI joint(l)	lumbar spinal a. L4(l)
Patient 8	**Embolized artery**
1. L2(r) (L1, L3)	lumbar spinal a. L2(r)
2. L2, L3	lumbar spinal a. L3(l,r) (including coiling)
Patient 9	**Embolized artery**
1. Th10, Th11(r)	intercostal a.(r) (including coiling)
2. Th10, Th11 (l)	intercostal a.(l)
3. skull	middle meningeal a. pre- and midbranch (tumor branches)
Patient 10	**Embolized artery**
1. L4(l)	lumbar spinal a. L4(l) (including microcoils) (distal/ proximal/tumor branches)
2. pelvis(r)	internal iliac a.(r) (including microcoil) (tumor branches)
3. L4	lumbar spinal a. L4(l)/lumbal a.
4. L2	lumbar spinal a. L2(l)/lumbalis a. (including coiling)
5. L3(l)	lumbar spinal a.
6. os ilium(r)	internal iliac a./proximal branch near internal iliac a.(r)/retroperitoneal branches at the transition of external iliac a. and femoralis communis a. (medial branch)
7. os ilium(r)	retroperitoneal iliac circumflex a.(tumor branches) / internal iliac a.(r) (tumor branches)
8. L4(l)	lumbar spinal a. L3(l)
9. L2(r)	lumbar spinal a. L3(r) (tumor branches)
10. L4	lumbar spinal a. L3(r) (tumor branches) and L4(l)
11. L3(r)	lumbar spinal a. L3(r) (tumor branches)
Patient 11	**Embolized artery**
1. L3	lumbar spinal a. L3(l,r) (including coiling)
2. L3	lumbar spinal a. L3(l)

Patient 12	Embolized artery
1. C4	truncus costocervicalis(r), coiling bifurcation and vertebral a.(l)
Patient 13	**Embolized artery**
1. C5-C6	truncus thyreocervicalis(l)

a, artery; r, right; l, left; L1-L5, lumbar vertebrae 1-5; Th5-Th7, Th10, Th11, thoracic vertebrae 5-7, 10, 11; C4-C6, cervical vertebrae 4-6.

Table 3. Individual data about additional therapies in the embolization group

Patient number	Sex	Age[a]	$T_xN_xM_x$	Histology	No. of embolizations	Locations	Cumulative I-131 (mCurie)	Additional therapies
1	Female	60	$T_2N_0M_1$	Follicular	11	1-11: pelvis	750	pelvis: 50 Gy, pelvis 8 Gy
2	Female	60	$T_1N_0M_1$	Follicular	3	1-3: L4	900	paravertebral and L4: 24 Gy, corporectomy L4
3	Female	68	$T_3N_0M_1$	Follicular	4	1,3: humerus, 2,4:ileum	750	pelvis: 8 Gy
4	Female	46	$T_2N_0M_1$	Follicular	1	1: 6th rib	900	excision ribmetastasis
5	Female	62	$T_2N_0M_1$	Follicular	7	1: Th6, 2: Th7, 3:shoulder, 4: Th6, 5: Th7, 6: pelvis/sacrum, 7: Th5	600	Th. 6, 7, 8: 24 Gy, Sac: 24 Gy, Th5:25 Gy
6	Female	65	$T_3N_0M_1$	Follicular	3	1-3: L3-4	750	-
7	Female	40	$T_4N_0M_1$	Follicular	12	1: pelvis and part L5, 2-12: pelvis	900	pelvis: 50 Gy, L1-3:30 Gy
8	Female	77	$T_3N_0M_1$	Follicular	2	1-2: L2	450	Th. 12-L4: 30 Gy
9	Female	54	$T_2N_0M_0$	Follicular	3	1: Th10, 2: Th11, 3: skull	650	Th. 5-12: 30 Gy, skull:30 Gy, skull:20 Gy
10	Male	35	$T_xN_0M_0$	Follicular	11	1: L4, 2: ileum, 3: L2, 4: L3, 5: L4, 6: ileum, 7: ileum, 8: L4, 9: L2, 10: L4, 11: L3	640	L1-L5: 8 Gy
11	Female	52	$T_xN_0M_1$	Follicular	2	1-2: L3	600	corporectomy L3
12	Female	45	$T_1N_0M_1$	Follicular	1	1: C4	450	corporectomy C4
13	Male	83	$T_xN_0M_1$	Follicular	1	1: C5/C6	150	surgical C5-C6

[a] Age a initial diagnosis (from duration of illness).
T, tumor; N, nodes; M, metastases.

Figure 1. *Angiogram before the embolization session of patient 11 (anterioposterior projection). Selective catheterization of the feeding lumbar artery on the left side shows a blush in the metastase of the third lumbar vertebra (L3).*

Figure 2A. *A sagittal T1-weighted image noncontrast enhanced of patient 11, showing a process in the third lumbar vertebra (L3) with destruction of the posterior wall of the corpus.*

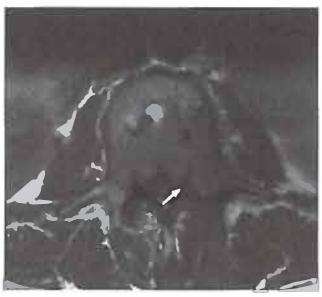

Figure 2B. *An axial T1-weighted image noncontrast enhanced, showing the same findings. Tumor extending into the pedicles bilaterally. Widening on the left side.*

Pre- and post-SET symptomology in patients with successful embolizations

Symptoms of patients comprised pain and neurological symptoms like numbness, tingling, or radicular pain. Symptoms decreased during 17 sessions, were unchanged during 8 sessions, and increased during 6 sessions ($p < 0.01$). The duration of improvement after these 17 sessions had a mean duration of 8.1 months with a range of 0.2-36 months. The most effective embolizations were performed at the first session. Most of the patients of whom the symptoms were unchanged after the session, did not have complaints before the embolization session.

Tg levels

In 23 of the 43 embolization sessions Tg levels were evaluable. Before embolization Tg levels ranged from 18 to 18,200 ng/ml and afterward from 13 to 37,400 ng/ml (Table 4). After the embolization, serum Tg levels decreased in 14 procedures (mean change, 1015 ng/ml) and increased in 9 procedures (mean change, 4932 ng/ml, not significant). The greatest changes in serum Tg after embolization were noted in patients with the higher serum Tg concentrations (Table 4).

Of the 14 patients who had a decrease in Tg level, 8 patients had symptomatic relief, 4 patients did not feel difference in their complaints, and 2 patients had an increase of symptomatic complaints. Of the nine patients who had an increase in Tg level, four patients had symptomatic relief, two patients did not feel difference in their complaints, and three patients had an increase of symptomatic complaints.

Table 4. Tg levels before and after embolization session

Patient	Tg level before embolization (ng/mL)	Tg level after embolization (ng/mL)
1.	11,000	2375
	178	202
	18,200	16,800
	16,800	37,400
2.	4365	2400
	18	13
3.	246	102
	67	70
5.	525	16
	1415	1730
6.	155	250
	250	827
7.	1240	379
	489	442
	1110	1098
8.	97	45
	50	14
9.	772	276
	214	198
10.	685	1280
	6910	25,350
	5460	9200
11.	65	17

Tg, thyroglobulin

Survival time in SET and non-SET patients

The survival expressed as median standardized survival time was not significantly different between the SET group, which was 0.43 (95% confidence interval (CI), 0.24-0.63), and the non-SET group, which was 0.56 (95% CI, 0.39-0.74).

Comparison of the patients with follicular thyroid cancer separately showed no significant difference, 0.42 (95% CI, 0.04 -0.80), in the survival between the patients with embolization therapy and the patients of the control group. Comparison of the standardized survival of the 13 patients from the embolization group with the 23 patients from the control group with M1 tumors also showed no difference, 0.42 (95% CI, 0.0-0.95).

Complications

During the first five embolization sessions no steroid coverage was added, and several minor complications occurred (temporary hypotension, postembolization syndrome, and local edema). Afterward, prednisolone was given 30 mg daily during two weeks, and then was tapered in two weeks. No complications were seen in the following 38 embolization sessions.

Discussion

Our series illustrated that embolization therapy can achieve palliation of pain and prevent neurological damage in a substantial number of patients with bone metastases from differentiated thyroid cancer, but in contrast to radical surgical removal of bone metastases (23), embolization therapy does not appear to improve survival. Based on serum Tg measurements taken weeks after this therapy, it appears that more than half of treated patients achieved a reduction of tumor burden. Life expectancy, however, is probably not influenced by embolization therapy. The changes in serum Tg after embolization therapy were highly variable, but a decrease was noted more often than an increase.

When embolization therapy was successful or partially successful, in 61% there was a decrease of the serum Tg level. To minimize a possible long-lasting effect of other treatments, we used in our analysis only those embolization sessions for patients who had received no additional therapy 28-49 days before and for the same period after their embolization sessions. It should be noted that the half-life of Tg in the circulation is 4 hours to 4 days (24-26). Therefore, as serum Tg was measured at least 10 days after embolization therapy, it seems unlikely that serum Tg reflected acute necrosis of infarcted tumor tissue. Our data suggest that Tg is a weak indicator of tumor necrosis after embolization. Embolization therapy appears to be beneficial in two ways. First, it appears to improve the quality of life in some patients. This is particularly important because the survival of patients with metastatic differentiated thyroid cancer (DTC) is relatively long. This conclusion is also supported by the study of Eustatia-Rutten et al. (12). They noted that a substantial percentage of patients had

improvement in clinical symptoms after embolization therapy, although some of these patients did not have tumor regression scored by Tg-level and/or imaging. In another study of four patients, Smit et al. (9) noted dramatic relief of neurological symptoms after embolization therapy of vertebral metastasis from differentiated follicular thyroid carcinoma. In a third study of van Tol et al. (11), there was improvement of symptoms in patients treated with embolization and radioiodine therapy, but this improvement was not significantly different compared to patients treated with radioiodine therapy alone. The present study is a larger one than our early preliminary study (11) of five patients with bone metastasis due to DTC. In that study, radioiodine therapy alone or radioiodine therapy combined with embolization therapy was used, and there was a significantly greater decrease in serum Tg in patients when the combination of embolization and radioiodine therapy was employed than radioiodine alone. In the current larger series we conclude that embolization therapy is beneficial in a substantial number of patients. In our patients, the clinical symptoms were evaluable in 31 embolization procedures. A decrease of clinical complaints was found in 55%. Embolization therapy has been shown to be a safe and effective noninvasive procedure, which is in this study is confirmed by the low treatment failure of only four embolizations, and can be combined with all other treatment options, and complications are not common (11,12).

The second advantage of embolization therapy is that it can be used to prepare selected patients for surgery of the targeted metastatic lesion. This was done in four of our patients. Metastatic thyroid lesions, especially in bones, are hypervascular. By means of preoperative embolization, the intraoperative blood loss can be reduced (10), as has been shown in metastatic renal cell carcinomas (27).

Irradiated metastases can also be embolized to decrease local tumor progression. Five patients in our series had been irradiated before embolization therapy, and this did not make the procedure more difficult.

The present study was not designed to determine the effect of SET on life expectancy because there were important clinical differences between SET and non-SET patients. Based on a comparison of these groups, however, it seems unlikely that SET has an important impact on life expectancy. This is not surprising because, for the most part, SET only targets a portion of the tumor burden. It is also consistent with other reports regarding SET as a treatment for thyroid and other cancers. Wirbel et al. (28) reported that preoperative embolization of spinal and pelvic metastases of different primary tumors, mostly renal cell carcinoma, had no influence on survival time. In the study of Bernier et al. (29), 34 of 109 (31%) patients with DTC received selective arterial embolization therapy as preoperative and/or palliative treatment for bone metastases. No improvement in survival was noted. In the future, specific systemic treatment modalities for patients with DTC and hematological spread disease might possibly be more effective to improve survival. For improvement of survival, an aggressive multidisciplinary approach has been advocated (30), but local thera-

pies for tumor control, like embolization therapy, are very valuable to the preservation of quality of life.

In conclusion, life expectancy in patients with metastatic disease is not improved by embolization therapy, but a significant effect on complaints and reduction of tumor burden was found. Embolization therapy can be used for tumor debulking, devascularization of tumor before surgery, and pain reduction, and can be combined with other treatment modalities such as radiation.

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Chapter 8

Summary, general discussion and future perspectives

SUMMARY AND GENERAL DISCUSSION

Generally, differentiated thyroid cancer (DTC), including papillary and follicular thyroid cancer, carries an excellent prognosis. Ten-year survival rates range between 83% and 98% (1,2). This favorable prognosis results from both the effective initial therapy and the generally indolent biological behavior of this tumor. Initial therapy consists of total thyroidectomy followed by high dose radioiodine therapy to eliminate microscopic residual or metastatic disease and subsequent lifelong thyroid hormone suppletion therapy. Despite the favorable general prognosis, recurrence rates are high, as up to 20% develop recurrent disease during follow-up. Recurrences may become clinically evident even after 20 years following this initial therapy. Therefore lifelong follow-up of thyroid cancer patients is recommended (3,4). Follow-up strategies should be able to identify patients with recurrent disease. However, a proper balance between the diagnostic yield of monitoring tests and the associated patient burden and medical costs should be maintained. In the previous chapters we evaluated different aspects of the follow-up of DTC aiming to contribute to the development of an optimal follow-up strategy. The results of these studies are summarized and discussed in the following sections.

Thyroglobulin measurement

In the follow-up, the measurement of serum thyroglobulin plays a central role. Thyroglobulin (Tg) is a very large and heterogeneous glycoprotein, produced by thyroid epithelial cells and serves as a physical backbone for thyroid hormone synthesis. Tg can be used as a tumor marker because thyroid cells are the only source of Tg in the human body (5). Therefore, the presence of Tg after total thyroidectomy and high dose radioiodine therapy indicates the presence of residual functional thyroid tissue or recurrent / persistent disease. As a very specific biomarker, Tg measurement should be as sensitive, accurate and precise as possible. Improving sensitivity is the main point of interest in the development of new Tg assays. Highly sensitive Tg assays may be able to measure Tg levels in the lower range, and therefore permit the discovery of recurrent disease at an earlier stage.

In chapter 2 we have illustrated the usefulness of a new highly sensitive Tg assay in the follow-up of DTC. Analytic performance of this immunochemiluminometric assay (ICMA) was characterized by high sensitivity, full automation and high reproducibility. When we introduced this assay in the clinic, we identified measurable Tg levels in 12 of 110 patients, while our conventional immunoradiometric (IRMA) assay showed no demonstrable Tg. Four of these 12 patients had clinical evidence of disease at the time of measurement, endorsing the potential for earlier disease detection with this assay. However, the significance of the low detectable Tg concentrations in the remaining eight patients in this study is unclear. Improved sensitivity of Tg assays might come at the expense of a decreased specificity (6). Accordingly, other studies evaluating new sensitive Tg assays have reported an increas-

ing number of patients with low but detectable Tg levels without any demonstrable disease (6,7). These low Tg levels can be related to residual thyroid tissue or recurrent thyroid cancer which is too small to be imaged. The sensitivity of these modern Tg assays might exceed the sensitivity of currently available imaging techniques. Low detectable Tg levels can give rise to possibly unnecessary concern and even excessive diagnostic testing (8). Moreover, the course of serum Tg levels over time is probably more important than one single serum Tg value (9) and this pattern should play a crucial role in clinical decision-making. Therefore, follow-up data of these patients are needed to interpret the value of these low Tg levels and determine accurate Tg cut-off levels which warrant further diagnostic testing (6).

Another explanation for these elevated Tg levels can be the presence of heterophilic antibodies (HAMA) or of other, non-specific antibodies. Interference of HAMA's in immunometric assays usually leads to false positive results in the absence of Tg, or if Tg is present to a false elevation in the measured Tg level. Rarely, HAMA's can also lead to false negative or falsely low results (8). Both interference from HAMA's as well as from Tg antibodies (TgAb) are major methodological problems of Tg measurement. In chapter 3, methods to detect this interference are studied.

Interference by thyroglobulin antibodies in thyroglobulin measurement

The reported prevalence of TgAb in DTC patients ranges from 10%-25% (10,11). TgAb can cause under- or overestimation of Tg level depending on the Tg assay format (12,13). Therefore, all sera sent for Tg measurement require adjunctive Tgab testing (14). Tg is not reliable in TgAb positive sera. Available methods for assessing TgAb interference are quantitative TgAb measurement by TgAb immunoassays and Tg recovery (TgR) testing. The discordance between Tg measurements made by a radioimmunoassay (RIA) versus an immunometric assays (IMA) is generally considered the methodological benchmark for interference by TgAb. But this is impractical because few RIA's are available (15) and radioimmunoassays are time-consuming.

Data about the clinical utility of methods for detecting Tg interference are presented in chapter 3. We used two quantitative TgAb assays (TgAb-ICMA and TgAb-microparticle enzyme immunoassay (TgAb-MEIA)) and a new Tg-ICMA with TgR (Nichols Advantage®) in 127 patients who were followed for DTC. Tg-RIA was used in a limited number of samples. We provided evidence that TgR testing has value complementary to that of quantitative TgAb measurement in the detection of interference in Tg measurement. Particularly in sera with low TgAb titers, TgR showed to be helpful. Normal TgR can mean the preservation of Tg as tumor marker in the follow-up of these patients. Additionally, in one patient overrecovery indicated the presence of falsely increased Tg level by HAMA. This was confirmed by undetectable Tg by RIA and IRMA (immunoradiometric assay).

Our results are in contrast with earlier studies, reporting that TgR testing failed to differentiate TgAb-positive and – negative sera and is consequently unreliable (11,16). Therefore,

our favorable results observed with the Nichols Advantage TgR assay cannot be transposed to other TgR assays. Further studies are needed to confirm the potential added value of TgR assays. Unfortunately, discontinuation of Nichols Institute Diagnostics impedes further research to confirm the potential added value of this specific TgR assay.

From a methodological point of view, the recovery method is an elegant method to assess the extent to which detection of endogenous Tg is blocked by interfering TgAb. In the presence of TgAb measured by a quantitative TgAb assay, the recovery result can indicate if Tg measurement interference is actually present. Benefit of a quantitative TgAb immunoassay is the possibility to use serial TgAb measurement as surrogate tumor marker. Several studies have shown that persistently elevated TgAb level may indicate the presence of recurrent disease (10,17,18,). Therefore, TgR and quantitative TgAb measurement can be considered as complementary diagnostic tests.

RhTSH stimulated Tg measurement in the long-term follow-up of DTC

Apart from the application of a highly sensitive Tg assay (chapter 2), another method to achieve higher sensitivity is measuring Tg during TSH stimulation. TSH promotes Tg synthesis in thyroid cells. TSH stimulation can be achieved by inducing hypothyroidism by stopping thyroid hormone suppletion. However, thyroid hormone withdrawal induces several complaints like fatigue, cold intolerance, dry skin and weight gain, and results in a significant decline in quality of life (19,20). In 1998, recombinant human TSH (rhTSH) was introduced as a practical tool during follow-up to achieve TSH stimulation for Tg measurement and radioiodine scanning without thyroid hormone withdrawal (21-23). A rhTSH procedure consists of an intramuscular rhTSH injection on day 1 and day 2. Tg levels are subsequently measured on day 5.

Diagnostic value of a sensitive Tg assay and RhTSH stimulated Tg measurement

Recommended strategies in the follow-up of DTC patients have been presented in international guidelines (24,25). The first evaluation will take place 6-12 months after thyroidectomy and radioiodine ablation in low-risk patients, and should consist of (rh)TSH stimulated Tg measurement and ultrasound of the neck (US). During the long-term follow-up, Tg is traditionally measured during thyroid hormone suppression therapy (Tg-on). The timing or necessity of subsequent (rh)TSH stimulated Tg measurement was uncertain (24,25); Tg-on measurement may fail to identify patients with relative small amounts of residual tumor.

It was especially questioned whether the recently developed highly sensitive Tg assays could eliminate the need for rhTSH stimulation (26,27). In chapter 4 we demonstrate that the use of a sensitive Tg assay has additional diagnostic yield over a conventional assay in the detection of recurrent disease in long-term follow-up for DTC and practically obviates the need for testing after rhTSH stimulation. In this prospective study, 121 clinically disease free patients were included. Sensitive Tg measurement in patients on suppression therapy

resulted in three patients with Tg ≥ 1.0 ng/ml and recurrence could be localized in two of them (neck lesion and mediastinal/paravertebral lesion). RhTSH stimulated Tg measurement resulted in an additional 17 of 118 patients with a Tg concentration above our established cut-off level of ≥ 1.0 ng/ml, and therefore were suspected for having recurrent disease. However, in only one patient subsequent imaging resulted in the localization of recurrent disease (supraclavicular lesion). We have followed the other 16 patients for four additional years, but no recurrence was found. In conclusion, the additional yield of rhTSH stimulated Tg measurement was one additional patient found to have a localized recurrence. We consider this too low to justify rhTSH stimulation in all patients during long-term follow-up, even more because it is conceivable that this patient anyhow would have been identified with regular serial Tg-on measurement with a sensitive Tg assay. Meanwhile, other studies, which were mainly retrospective evaluations, have confirmed the limited value of periodic rhTSH stimulated Tg measurement in long-term follow-up (28-30).

Follow-up strategies for DTC are determined according to the initially assessed risk of recurrence. It has been suggested that rhTSH stimulated Tg measurement is unnecessary in low-risk patients but might be useful in high-risk patients (30). This discussion is complicated because multiple schemes for risk stratification are in use with different definitions of low and high-risk. Moreover the established risk factors and staging systems often fail in predicting who will develop a recurrence or die of tumor, and still also patients in the lowest risk group die of thyroid cancer (31,32). Part of this failure is explained by the absence of "the response to initial therapy" as a prognostic factor in staging systems (33,34), which seems contra-intuitive and confirms the limitations of staging systems. In our study we therefore disregarded classification into low- and high-risk subgroups and included patients regardless of risk of recurrence or follow-up duration. By doing so, this study population consisted of a mixture of low- and high-risk patients, reflecting the variety of patients in follow-up for DTC in daily clinical practice. Recurrence was found by using the sensitive Tg assay in one low- and one high-risk patient (35), one additional recurrence in a low-risk patient was found by using rhTSH stimulated Tg measurement. Consequently, we conclude that for both low- and high- risk patients the added diagnostic value of rhTSH stimulated Tg measurement is minimal and long-term follow-up should be based on serial Tg-on measurement with a sensitive Tg assay. Currently, most authors (30,36,37) conclude that periodic Tg testing after TSH stimulation is needed in high-risk patients, although the evidence supporting this recommendation is very limited and well-conducted prospective studies are lacking. There is an urgent need for more research to develop true evidence-based follow-up guidelines, tailored according to the risk at recurrence.

Impact of the use of rhTSH stimulated Tg measurement on quality of life.
Traditionally, primary outcome measures in cancer care are survival and disease free survival. Consequently in the follow-up of cancer, the sensitivity and specificity of monitoring methods for detection of recurrent disease are considered of central importance.

But there has been growing recognition that patient-reported outcome measures, in particular measures of quality of life (QOL) convey important additional information in cancer care. Since patient with DTC are submitted to lifelong follow-up, careful consideration of the impact of monitoring methods on QOL is essential. Unfortunately, very little is known about the influence of follow-up testing on quality of life of DTC patients. New monitoring methods are often introduced without evaluating the associated patient burden when using these tests.

Therefore, we examined the impact of the rhTSH stimulation procedure and the subsequent additional diagnostic tests on psychological distress, anxiety and cancer worries. The results have been presented in chapter 5, and clearly demonstrate that the rhTSH stimulation procedure has a significant negative impact on psychological health in those patients who turn out to have an increased Tg level, and will undergo additional diagnostic investigations. As expected, these patients showed a temporary increase in psychological distress and higher level of anxiety compared to baseline and Tg negative patients. Moreover, worries about thyroid cancer increased after the procedure. These cancer worries remained higher compared with Tg negative patients after being informed about imaging results, although the majority of these Tg positive patients (85%) had favorable imaging results and no recurrence could be localized.

Since the use of rhTSH resulted in a positive rhTSH-Tg test but no localized recurrence in 13% of all participants, prevailing cancer worries will be an important adverse psychological consequence in a substantial amount of patients. This is even more serious, knowing that after four years follow-up in none of these patients clinical evidence for recurrence was found.

This is the first study evaluating the influence of the rhTSH procedure on QOL in the follow-up of DTC. The demonstrated unfavorable effect on psychological health should be an important issue in the evaluation of the use of rhTSH. Moreover, with the ongoing development of laboratory measurements and imaging techniques as monitoring methods for DTC, increasing awareness is needed for the impact of their use on QOL.

Cost-effectiveness of rhTSH stimulated Tg measurement
As the follow-up of DTC is lifelong and the estimated prevalence of DTC worldwide is 475.200, considerable medical costs are generated (38). With restricted health care resources, evaluating costs and effects of a monitoring method in this follow-up is crucial. In chapter 6, the cost-effectiveness of the rhTSH procedure and of Tg measurement during thyroid hormone suppression therapy (Tg-on) are compared. As mentioned earlier, the extra procedure

resulted in the detection of one additional patient with localized recurrent disease. The cost-effectiveness ratio was €192.961, which means that an extra €192.961 had to be invested with the rhTSH protocol to detect one additional patient with localized recurrence compared to the Tg-on protocol. These high costs were due to the expensive injection in itself (€1232) and secondly due to the large amount of additional diagnostic procedures which were required to establish the location of the recurrence and treat it with radioactive iodine. In the study protocol (see chapter 4), the Tg cut-off value (1.0 ng/ml) for addition imaging was stringent and extensive imaging (neck ultrasound, 150 mCurie radioionine treatment + posttherapy I-131 whole body scan, FDG-PET, on indication: CT/MRI/ octrotide scan) was performed.

Even if we increased our Tg cut-off value (2.0 ng/ml) and used limited imaging (neck ultrasound, 150 mCurie radioionine treatment + posttherapy I-131 whole body scan), the costs to detect one additional patient by using rhTSH were still very high (€151.226). The unfavorable cost-effectiveness ratio, in addition to the limited diagnostic yield (chapter 4) and negative influence on QOL (chapter 5) precludes the use of rhTSH stimulated Tg measurement in the long-term follow-up of DTC.

Embolization of bone metastases from differentiated thyroid cancer

As previously mentioned, generally differentiated thyroid cancer, carries an excellent prognosis. However, patients with persistent disease have a life expectancy of approximately 60% of the residual life span (2). In these patients, therapy is aimed at the improvement of survival and quality of life. In DTC patients with bone metastases, selective embolization therapy is one of the treatment options. In chapter 7, we evaluated the effect of selective embolization therapy on life expectancy, symptoms and serum thyroglobulin level in 13 DTC patients (31 embolization sessions). Embolization therapy could achieve palliation of pain, reduction of neurological symptoms and reduction of tumor burden (based on decreasing Tg levels). Survival time was not influenced by embolization therapy. Considering the relatively long survival of patients with metastatic DTC, this achieved improvement of quality of life is an important result.

Future perspectives

Differentiated thyroid carcinoma is a relatively rare disease with a prolonged course, consequently prospective randomized clinical trials of treatment and follow-up methods of DTC are lacking (3). However, the excellent prognosis in most patients and lifelong follow-up implies a large number of patients in follow-up for DTC worldwide. Therefore, any changes in follow-up schedules and procedures may have a major human and economic impact. A lot of effort is put in the development of diagnostic methods for earlier identification of patients with recurrent DTC. However, DTC is a relatively benign disease with generally

a slow course and there is no evidence to support that earlier identification and intervention in these patients ultimately will affect mortality (39). This is important to realize, since monitoring patients is not always harmless. As presented in this thesis, rhTSH stimulated Tg measurement seriously affected the psychological well-being in a significant amount of Tg positive patients in whom ultimately no recurrence was found. Likewise, this is a potential drawback of the new highly sensitive Tg assays. We might uncover minimal disease in patients who will never develop clinically significant disease. Appropriate use of monitoring methods, on the right moment, in the right patients is essential. The focus in the follow-up of DTC should not be on finding occult disease but on identifying patients in whom DTC likely shorten their lives (40). The advent of the previously mentioned highly sensitive Tg assays is one of the major developments in the follow-up care of DTC patients. As shown in chapter 4, the introduction of a sensitive chemiluminiscence immunoassay can result in the earlier detection of patients with recurrence, who were not yet identified using a conventional Tg assay. The current drawback of these assays is the detection of low levels of Tg in a substantial amount of patients, who have no demonstrable disease activity by imaging. Follow-up studies of these assays are needed to determine the significance of these low Tg levels. Subsequently, Tg cut-off levels for diagnostic testing should be established to avoid unnecessary diagnostic testing and treatment. Moreover, in cases of only slightly elevated Tg, the strongest indication for recurrence is still an increasing serum Tg level within the same patient rather than a single value (41). Therefore, the slope of serum Tg levels should play in important role in clinical decision making. This will warrant the appropriate use of these highly sensitive assays, attributing to an optimal follow-up of DTC patients.

Despite the introduction of the CRM-457 reference preparation (42,43), the variability of results using differing Tg assays remains substantially and can differ by a factor three to four (44). Future development of harmonization samples is needed to reduce this interassay variability (44). Moreover, wide interassay variation limits the applicability of absolute Tg cut-off levels mentioned in guidelines for the follow-up of DTC (25,36,45). Therefore, institutional Tg cut-off values should be defined (44,46).

TgAb interference is another important methodological problem of Tg measurement. Unfortunately, the new Tg assays are still hampered by TgAb interference, rendering Tg measurement unreliable for follow-up in patients with TgAb. Presumably, Tg assays without any TgAb interference will not be available in the near future. Therefore, the attention should be focused on the development of reliable methods to detect TgAb interference. In the future, simultaneously use of Tg recovery testing and quantitative TgAb measurement might be the best approach for the accurate detection of interference in Tg measurement. Unfortunately, the TgR assay evaluated in this thesis is not available anymore and few new TgR methods are developed. In view of the presented favorable results, the value of TgR should be reconsidered. Development of accurate TgR assays will simplify the follow-up management of TgAb positive patients. Additionally, the value of TgAb levels as surrogate

marker of disease activity in TgAb positive patients should be explored in depth. An increasing level of TgAb might reflect enhanced presentation of thyroid tumor antigens to the immune system (11). Long-term prospective follow-up studies evaluating the use of serial TgAb measurement in DTC patients are needed to confirm this hypothesis.

Considering the described complexity of the measurement of Tg and TgAb interference, centralization of these analyses to centers with the necessary expertise is preferable. Centralization of laboratory testing will make it possible to establish Tg cut-off values, generally applicable to all DTC patients treated in the affiliated hospitals.

Recombinant human TSH (rhTSH) was introduced as a practical tool in the follow-up of DTC to enhance TSH stimulation for Tg measurement and diagnostic radioiodine whole body scans (dWBS) without the need for thyroid hormone withdrawal. Nevertheless, the need for rhTSH stimulated Tg measurement in the long-term follow-up can be questioned, as demonstrated in this thesis and by other studies (28-30). Additionally, the sensitivity of dWBS has shown to be low and is nowadays often omitted in follow-up (47,48). Consequently, the value of rhTSH for Tg measurement in long-term follow-up and diagnostic radioiodine whole body scans is limited. However, promising applications of rhTSH are rhTSH aided FDG-PET and radioiodine ablation therapy. RhTSH is definitely valuable in preserving quality of life as opposed to thyroid hormone withdrawal, so potential indications deserve careful exploration.

Follow-up strategies for low-risk DTC patients (70-85% of the DTC patients) are well-defined. It is generally accepted that high-risk patients need more intensive follow-up but clear evidence based follow-up strategies for these patients are lacking. Moreover, current staging systems are not always correctly predicting outcome. Restaging of patients on the basis of the response to initial therapy, referred to as ongoing risk assessment, will result in a more correct prediction of the risk of recurrence (34). Additionally, molecular characterization may be useful in risk stratification. In the last decades there has been a significant improvement in the knowledge of molecular alterations involved in DTC. Molecular characterization of aggressive versus non-aggressive DTC may be a valuable tool to individualize treatment and follow-up. In the future, ongoing risk assessment and molecular characterization of DTC should be used for the development of more accurate risk staging systems. This will result in follow-up protocols tailored to the individual risk at recurrence.

A minority of patients experience progressive life threatening growth and metastatic spread of DTC. Local treatment options, as embolization of bone metastases, are valuable in reducing symptoms. Unfortunately, systemic treatment options for advanced radioiodine resistant DTC to improve survival are limited. Results of chemotherapy are disappointing until now. However, recent advances in molecular oncology have led to the development of promising agents targeting growth factors, intracellular receptor kinases and downstream mediators of cell signaling. Some of these novel agents, for example Axitinib and Sorafenib,

both tyrosine kinase inhibitors, have yet shown clinically relevant antitumor activity in patients with metastatic thyroid carcinoma in phase II trials (49,50).

In conclusion, the follow-up and treatment of differentiated thyroid carcinoma is an evolving field. At a time of increased sensitivity of monitoring tests in the follow-up of DTC, identifying patients for whom these tests are clinically beneficial is essential to limit patient burden and medical costs. Genotypical characterization might have the potential to tailor therapy and follow-up to the individual patient. The results of ongoing clinical trials to assess the clinical value of genetic mutation testing for prognostic stratification and the long-term efficacy of new therapies, are eagerly awaited.

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Samenvatting, discussie en vooruitblik

Samenvatting en discussie

Gedifferentieerd schildkliercarcinoom, dat bestaat uit papillair en folliculair schildkliercarcinoom, heeft over het algemeen een uitstekende prognose. De 10-jaars overleving varieert van 83% tot 98% (1,2). Deze gunstige prognose is een gevolg van de effectieve initiële therapie en het, over het algemeen, indolente biologische gedrag van deze tumor. De initiële therapie bestaat uit totale thyreoidectomie gevolgd door een behandeling met een hoge dosis radioactief jodium om microscopische residuele ziekte dan wel metastasen te elimineren. Vervolgens wordt levenslang schildklierhormoon substitutietherapie gegeven. Ondanks deze gunstige prognose is het aantal recidieven hoog, tot 20% van de patiënten ontwikkelt een recidief in de follow-up. Deze recidieven kunnen zelfs 20 jaar na initiële therapie ontdekt worden. Daarom wordt levenslange follow-up van patiënten met schildkliercarcinoom geadviseerd (3,4).

De follow-up strategie moet in staat zijn patiënten met een recidief van gedifferentieerd schildkliercarcinoom te identificeren. Hierbij moet echter wel een juiste balans zijn tussen de diagnostische opbrengst van de onderzoeksmethoden, de belasting voor de patiënt en de medische kosten. In de voorgaande hoofdstukken zijn verschillende aspecten betreffende de follow-up van gedifferentieerd schildkliercarcinoom onderzocht, om hiermee een bijdrage te leveren aan de ontwikkeling van een optimale follow-up strategie. De resultaten van deze studies worden samengevat en besproken in de volgende paragrafen.

Thyreoglobuline meting

Het bepalen van het thyreoglobuline (Tg) speelt een centrale rol in de follow-up van gedifferentieerd schildkliercarcinoom. Tg is een groot en heterogeen glycoproteïne en wordt geproduceerd door epitheliale cellen in de schildklier en dient als een matrixeiwit voor de schildklierhormoonsynthese. Tg kan als een tumormerkstof worden gebruikt omdat schildkliercellen de enige bron van Tg in het menselijk lichaam zijn (5). Hierdoor wijst de aanwezigheid van Tg, na thyreoidectomie en hoge dosis radioactief jodium therapie, op achtergebleven functionerend schildklierweefsel dan wel recidief / persisterende ziekte. De Tg bepaling moet sensitief, accuraat en precies zijn. Het optimaliseren van de sensitiviteit is een van de belangrijke aandachtspunten in de ontwikkeling van nieuwe Tg methodes. Ultrasensitieve Tg bepalingen kunnen lagere Tg concentraties meten en hierdoor een recidief in een vroeger stadium aantonen.

In hoofdstuk 2 beschrijven we de waarde van een nieuwe ultrasensitieve Tg meting in de follow-up van gedifferentieerd schildkliercarcinoom. Analytische eigenschappen van deze immunochemiluminometrische meetmethode (ICMA) zijn de hoge sensitiviteit, de volautomatische werking en de hoge reproduceerbaarheid. Bij de introductie van deze meetmethode in de kliniek, bleek er sprake van een aantoonbaar Tg in 12 van 110 patiënten die tevoren een

niet aantoonbaar Tg hadden met een conventionele immunoradiometrische meetmethode (IRMA).

Vier van deze 12 patiënten hadden klinische aanwijzingen voor een recidief op het moment van Tg meting. Deze bevinding ondersteunt de mogelijkheid om met deze meetmethode eerder een recidief te detecteren. Echter, de betekenis van de lage aantoonbare Tg concentraties in de resterende acht patiënten in deze studie is nog niet duidelijk. De verbeterde sensitiviteit van Tg bepalingen zou ten koste kunnen gaan van de specificiteit (6). In overeenkomst met deze studie, rapporteerden ook andere studies die nieuwe sensitieve Tg meetmethoden evalueerden een groot aantal patiënten met lage Tg concentraties zonder aantoonbare ziekte (6,7). Deze lage Tg concentraties kunnen duiden op resterend schildklierweefsel of een recidief schildkliercarcinoom dat te klein is om afgebeeld te kunnen worden. De sensitiviteit van de moderne Tg meetmethodes lijkt de sensitiviteit van de op dit moment beschikbare afbeeldende technieken te overtreffen. Deze lage Tg concentraties kunnen aanleiding zijn voor onnodige onrust en overmatige diagnostiek bij deze patiënten (8). Bovendien is het beloop van de serum Tg waarde in de tijd belangrijker dan een individuele Tg waarde en moet dit een cruciale rol spelen in klinische beslissingen. Follow-up data van de patiënten met lage Tg concentraties zonder klinische aanwijzingen voor een recidief zijn nodig om de waarde van deze lage Tg concentraties te bepalen en om een accurate Tg afkapwaarde vast te stellen waarboven aanvullend onderzoek zinvol is (6).

De aanwezigheid van heterofiele antilichamen (HAMA) of andere niet-specifieke antilichamen kan ook een verklaring zijn voor een aantoonbaar Tg. Interferentie van HAMA's in immunometrische meetmethodes leidt over het algemeen tot foutpositieve resultaten als er geen Tg aanwezig is, of een foutieve verhoging van de gemeten Tg concentratie als er Tg aanwezig is. In zeldzame gevallen kunnen HAMA's ook leiden tot foutnegatieve of foutief verlaagde resultaten (8). De interferentie van HAMA's en ook aanwezigheid van Tg antistoffen (TgAb) zijn belangrijke methodologische problemen bij Tg metingen. In hoofdstuk 3 worden methodes om deze interferentie te detecteren beschreven.

Interferentie door thyreoglobuline antilichamen in de thyreoglobuline meting

De prevalentie van thyreoglobuline antistoffen (TgAb) varieert tussen de 10% en 25% (10,11). Deze TgAb kunnen onder- of overschatting van de Tg concentratie veroorzaken, afhankelijk van de gebruikte Tg methode (12,13). Elke Tg meting moet dan ook gepaard gaan met een TgAb meting (14) aangezien een Tg uitslag bij een patiënt met TgAb onbetrouwbaar is. Beschikbare methodes voor het bepalen van TgAb interferentie zijn kwantitatieve TgAb metingen met behulp van TgAb immunoassays en Tg recovery (TgR) metingen. Bij de Tg recovery (Tg terugvindingsmethode) wordt een monster verrijkt met exogeen Tg. Na meting van het basale en verrijkte monster kan berekend worden wat het percentage teruggevonden Tg (recovery) is. Discordantie tussen een Tg meting met een radioimmunoassay (RIA) en Tg meting met een immunometrische assay (IMA) wordt beschouwd als de gouden standaard

voor TgAb interferentie. Echter, Tg RIA's zijn tijdrovend en beperkt beschikbaar (15) en daarom niet praktisch in gebruik.

In hoofdstuk 3 worden data over de klinische toepasbaarheid van verschillende methodes voor detectie van TgAb interferentie besproken. Twee kwantitatieve TgAb bepalingen (TgAb-ICMA en TgAb-microparticle enzyme immunoassay (TgAb-MEIA)) en een nieuwe Tg-ICMA bepaling met TgR (Nichols Advantage®) werden gebruikt bij 127 patiënten in follow-up voor gedifferentieerd schildkliercarcinoom. De Tg-RIA bepaling werd in een beperkt aantal monsters gebruikt omdat deze methode niet beïnvloed lijkt te worden door TgAb. De TgR meting bleek aanvullende waarde te hebben naast kwantitatieve TgAb meting bij de detectie van interferentie in de Tg meting. De TgR meting was voornamelijk bijdragend in sera met lage TgAb titers. Indien de TgR normaal is, blijft de Tg concentratie bruikbaar als tumormerkstof in de follow-up van deze patiënten. Een sterk verhoogde recovery uitslag wees op een vals verhoogde Tg concentratie door HAMA's. Een onmeetbaar Tg in de RIA en IRMA (immunoradiometric assay) bevestigde dit vermoeden.

Deze resultaten komen niet overeen met eerdere studies, waarin TgR bepalingen TgAb positieve en TgAb negatieve sera niet konden onderscheiden en daarom als onbetrouwbaar werden beschouwd (11,16). De gunstige resultaten met de Nichols Advantage TgR assay kunnen dan ook niet geëxtrapoleerd worden naar andere TgR bepalingen en verder onderzoek is nodig om de toegevoegde waarde van TgR meting te bevestigen.

Vanuit een methodologisch oogpunt, is de recovery bepaling een elegante methode om interferentie in de Tg meting door TgAb te bepalen. Indien een kwantitatieve TgAb bepaling TgAb heeft aangetoond, kan de TgR assay aangeven of er daadwerkelijk sprake is van interferentie in de Tg meting. Het voordeel van een kwantitatieve TgAb bepaling is de mogelijkheid om seriële TgAb metingen te gebruiken als een surrogaat tumormerkstof. Meerdere studies hebben aangetoond dat persisterend verhoogde TgAb concentraties kunnen duiden op de aanwezigheid van een recidief (10,17,18). TgR en kwantitatieve TgAb metingen dienen daarom als beschouwd te worden als complementaire diagnostische testen

RhTSH gestimuleerde Tg meting in de lange termijn follow-up van gedifferentieerd schildkliercarcinoom

Naast het gebruik van een ultrasensitieve Tg assay (hoofdstuk 2), kan een Tg meting tijdens TSH stimulatie een hogere sensitiviteit geven. TSH stimuleert de synthese van Tg in schildkliercellen. TSH stimulatie kan worden bereikt door het induceren van hypothyreoïdie door het staken van de schildklierhormoonsuppletie. Echter, hypothyreoïdie geeft klachten van vermoeidheid, koude intolerantie, een droge huid, gewichtstoename en een significante daling van de kwaliteit van leven (19,20). In 1998 werd recombinant humaan TSH (rhTSH) geïntroduceerd als middel om TSH stimulatie te verkrijgen voor Tg metingen en radioactief jodium scans zonder het staken van schildklierhormoon (21-23). De procedure van een

rhTSH gestimuleerde Tg meting bestaat uit een intramusculaire rhTSH injectie op dag 1 en dag 2, en vervolgens een bepaling van de Tg concentratie op dag 5.

Diagnostische waarde van een sensitieve Tg assay en rhTSH gestimuleerde Tg meting

In verschillende internationale richtlijnen wordt de follow-up van patiënten met gedifferentieerd schildkliercarcinoom beschreven (24,25). De eerste evaluatie vindt bij laag-risico patiënten 6-12 maanden na thyreoidectomie en ablatie met radioactief jodium plaats en bestaat uit (rh)TSH gestimuleerd Tg meting en een echografie van de hals. In de lange termijn follow-up wordt Tg over het algemeen tijdens schildklierhormoon substitutietherapie (Tg-on) gemeten. Het moment en de noodzaak van (rh)TSH gestimuleerde Tg metingen in deze fase was echter onzeker (24,25); Tg-on meting zou mogelijk patiënten met een klein volume residuele tumor niet kunnen identificeren. Het was onduidelijk of de recent ontwikkelde ultrasensitieve Tg bepalingen het gebruik van rhTSH stimulatie overbodig zouden maken.

De data gepresenteerd in hoofdstuk 4 tonen de toegevoegde waarde van een ultrasensitieve Tg assay in vergelijking met een conventionele Tg assay, voor de detectie van patiënten met een recidief in de lange termijn follow-up van gedifferentieerd schildkliercarcinoom. Hierbij bleek rhTSH gestimuleerde Tg meting overbodig. In deze prospectieve studie werden 121 patiënten geïncludeerd zonder klinisch aanwijzing voor een recidief. Een sensitieve Tg meting tijdens suppressietherapie resulteerde in het aantonen van een Tg ≥ 1.0 ng/ml bij drie patiënten, bij twee van deze patiënten kon een recidief schildkliercarcinoom worden gelokaliseerd (tumor recidieven in de hals en mediastinaal/paravertebraal). De rhTSH gestimuleerde Tg meting in de overige 118 patiënten gaf bij 17 extra patiënten een Tg ≥ 1.0 ng/ml, mogelijk wijzend op een recidief schildkliercarcinoom. Echter, slechts in een één patiënt werd bij aanvullend beeldvormend onderzoek een recidief gelokaliseerd (supraclaviculair). De overige 16 patiënten zijn inmiddels 4 jaar vervolgd. Bij geen van hen is een recidief gelokaliseerd. Concluderend was de toegevoegde waarde van rhTSH gestimuleerde Tg meting de opsporing van één extra patiënt met een gelokaliseerd recidief. Naar onze mening is deze opbrengst te beperkt om rhTSH stimulatie in de gehele groep patiënten in follow-up voor gedifferentieerd schildkliercarcinoom te rechtvaardigen. Zeker aangezien het te verwachten is dat een seriële Tg-on meting met een sensitieve Tg assay ook zou hebben geleid tot het vaststellen van dit recidief. Intussen hebben andere, voornamelijk retrospectieve studies, eveneens de beperkte waarde van rhTSH gestimuleerde Tg meting in de lange termijn follow-up van gedifferentieerd schildkliercarcinoom laten zien (28-30).

Bij de plaatsbepaling van rhTSH in de follow-up speelt de initiële risico stratificatie een belangrijke rol. De waarde van een rhTSH gestimuleerde Tg meting zou vooral zinvol kunnen zijn in bepaalde categorieën hoog-risico patiënten (30). Echter het gebruik van multipele risicostratificatie systemen waarin laag-risico en hoog-risico verschillend gedefinieerd wordt, maakt deze discussie en de daaraan gekoppelde plaats voor rhTSH in de follow-up

zeer gecompliceerd. Bovendien zijn de risicostratificatie systemen die nu gebruikt worden slechts beperkt in staat te voorspellen wie een recidief zal ontwikkelen en overlijden ook patiënten in de laag-risico groep aan schildkliercarcinoom (31,32). Dit wordt deels verklaard door de afwezigheid van de "respons op initiële therapie" als prognostische factor in de stadiëring (33,34). Gezien bovenstaande onduidelijkheden werden in onze studie patiënten ongeacht hun stadiering of follow-up duur geïncludeerd. Hierdoor bestond de studiepopulatie uit zowel laag en hoog-risico patiënten, representatief voor de variëteit van patiënten in follow-up voor gedifferentieerd schildkliercarcinoom in de dagelijkse praktijk. Het gebruik van de sensitieve Tg assay resulteerde in de lokalisatie van een recidief in één hoog-risico en één laag-risico patiënt (35), één extra recidief bij een laag-risico patiënt werd gelokaliseerd met behulp van rhTSH. Hieruit kunnen we concluderen dat voor zowel laag als hoog-risico patiënten de aanvullende waarde van rhTSH gestimuleerde Tg meting minimaal is. De lange termijn follow-up zou dan ook gebaseerd moeten zijn op seriële Tg-on meting met een sensitieve Tg bepaling. Echter, op dit moment wordt door meerdere auteurs (30,36,37) TSH gestimuleerde Tg meting nodig geacht in hoog-risico patiënten. De bewijsvoering hiervoor is beperkt en goede prospectieve studies onderbreken. Er is dan ook een dringende behoefte aan nieuwe studies om te komen tot wetenschappelijk onderbouwde follow-up richtlijnen toegespitst op het recidief risico van de individuele patiënt.

Invloed van het gebruik van rhTSH gestimuleerde Tg meting op de kwaliteit van leven

De traditionele primaire uitkomstmaten in de zorg voor patiënten met kanker zijn overleving en ziektevrije overleving. De sensitiviteit en specificiteit van diagnostische testen voor de detectie van een recidief worden dan ook essentieel geacht. Kwaliteit van leven wordt echter steeds meer gezien als een belangrijke uitkomstmaat in de oncologische zorg. Aangezien patiënten met schildkliercarcinoom levenslang in follow-up blijven is aandacht voor de impact van gebruikte diagnostische testen in de follow-up op de kwaliteit van leven van groot belang. Helaas is hier weinig over bekend. Nieuwe testen in de follow-up worden vaak geïntroduceerd zonder evaluatie van de belasting voor de patiënt.

Wij onderzochten de invloed van een rhTSH stimulatie procedure en de hieruit volgende verdere diagnostiek op psychologische distress (psychologische reacties die gepaard gaan met negatieve gevoelens als angst en somberheid), angst en zorgen over kanker. De resultaten van deze studie, beschreven in hoofdstuk 5, laten een duidelijke negatieve invloed zien van de rhTSH stimulatie procedure op de kwaliteit van leven van patiënten met een aantoonbaar Tg die aanvullend onderzoek moesten ondergaan. Bij deze patiënten werd een tijdelijke stijging van psychologische distress, angst en zorgen over kanker waargenomen in vergelijking met controle groep van patiënten die na rhTSH stimulatie geen aantoonbaar Tg hadden (Tg negatieve patiënten). Tg positieve patiënten hielden na de uitslag van de aanvullende diagnostiek meer zorgen over kanker vergeleken met Tg negatieve patiënten, ondanks

dat de meerderheid van deze Tg positieve patiënten (85%) een gunstige uitslag had en geen recidief kon worden aangetoond.

Het gebruik van rhTSH resulteerde in een positieve rhTSH-Tg test zonder gelokaliseerde tumor activiteit bij 13% van de gehele studiepopulatie. Persisterende zorgen over kanker zijn dan ook een belangrijk negatief effect. Zeker, wanner na vier follow-up nog steeds bij geen van deze patiënten klinische aanwijzingen voor een recidief zijn gevonden.

Dit is de eerste studie waarin de invloed van de rhTSH procedure op de kwaliteit van leven van patiënten in de follow-up voor gedifferentieerd schildkliercarcinoom is onderzocht. De ongunstige invloed op psychische distress, angst en zorgen over kanker dient een belangrijke rol te spelen in de evaluatie van het gebruik van rhTSH. De verdere ontwikkelingen van laboratorium bepalingen en beeldvormende technieken maken het noodzakelijk ook het effect hiervan op de kwaliteit van leven te evalueren.

Kosteneffectiviteit van rhTSH gestimuleerde Tg meting

De levenslange follow-up en het grote aantal patiënten wereldwijd met gedifferentieerd schildkliercarcinoom (geschatte prevalentie 475.200) leiden tot aanzienlijke medische kosten (38). Gezien de sterk stijgende kosten van de gezondheidszorg, is evaluatie van de kosteneffectiviteit van diagnostische testen cruciaal. In hoofdstuk 6 wordt de kosteneffectiviteit van de Tg meting na rhTSH stimulatie vergeleken met de Tg meting tijdens het gebruik van schildklierhormoon substitutietherapie (Tg-on). Zoals beschreven in hoofdstuk 4 heeft het gebruik van rhTSH een beperkt resultaat (het leidde slechts tot de opsporing van één extra patiënt met een gelokaliseerd recidief). De kosteneffectiviteitratio was €192.961, dit betekent dat met het gebruik van rhTSH €192.961 extra moet worden geïnvesteerd om bij één extra patiënt een gelokaliseerd recidief vast te stellen, vergeleken met de Tg-on meting. Deze hoge kosten worden verklaard door enerzijds de prijs van de rhTSH injectie (€1232) en anderzijds het grote aantal aanvullende onderzoeken (inclusief een behandeling met hoge dosis radioactief jodium) dat nodig was om de locatie van het recidief vast te stellen.

In het studieprotocol (zie hoofdstuk 4) werd een relatief lage Tg afkapwaarde (1.0 ng/ml) voor aanvullend onderzoek gebruikt. Daarnaast was het aanvullend onderzoek uitgebreid, bestaande uit een echografie van de hals, behandeling met 150 mCurie radioactief jodium gevolgd door een diagnostische posttherapie scan, FDG-PET en op indicatie CT, MRI of een octreotide scan. Echter, wanneer een hogere Tg afkapwaarde (2.0 ng/ml) zou worden gebruikt, gecombineerd met beperkt aanvullend onderzoek slechts bestaand uit een echografie van de hals en een behandeling met 150 mCurie radioactief jodium gevolgd door een diagnostische posttherapie scan, dan bleven de kosten nodig om één extra patiënt met een recidief te vinden nog steeds erg hoog (€151.226). De ongunstige kosteneffectiviteitratio, de beperkte diagnostische opbrengst (hoofdstuk 4) en de negatieve invloed op de kwaliteit van leven (hoofdstuk 5) maken dat er geen plaats is voor routinematig rhTSH gestimuleerde Tg meting in de lange termijn follow-up van patiënten met gedifferentieerd schildkliercarcinoom.

Embolisatie van botmetastasen van gedifferentieerd schildkliercarcinoom

Zoals eerder genoemd heeft gedifferentieerd schildkliercarcinoom over het algemeen een uitstekende prognose. De levensverwachting van patiënten met persisterende ziekte is echter 60% van de oorspronkelijke levensverwachting (2). Behandeling van deze patiënten is dan ook gericht op verlenging van overleving en kwaliteit van leven. Bij patiënten met botmetastasen van gedifferentieerd schildkliercarcinoom behoort selectieve embolisatie van de voedende bloedvaten van een metastase tot de behandelmogelijkheden. In hoofdstuk 7 evalueren we de effecten van selectieve embolisatie therapie op de levensverwachting, symptomen en de Tg concentratie van 13 patiënten met gedifferentieerd schildkliercarcinoom bij wie in totaal 31 embolisatieprocedures werden verricht. De levensverwachting werd vergeleken met een historische controle groep patiënten met persisterende ziekte dan wel terugkeer van schildkliercarcinoom na de initiële behandeling. Embolisatie leidde tot een afname van pijn en neurologische symptomen en afname van tumormassa (gebaseerd op een daling van de Tg concentratie) maar had geen invloed op de overleving. Gezien de relatieflange overleving van patiënten met gemetastaseerd gedifferentieerd schildkliercarcinoom is vooral de verbetering van kwaliteit van leven een belangrijk resultaat.

Vooruitblik

Gedifferentieerd schildkliercarcinoom is een relatief zeldzame aandoening met een langdurig beloop waardoor prospectieve gerandomiseerde klinische onderzoeken gericht op de behandeling en follow-up ontbreken (3). Echter, door de over het algemeen uitstekende prognose en de levenslange follow-up zijn er wereldwijd een groot aantal patiënten in follow-up voor gedifferentieerd schildkliercarcinoom. Een verandering in de follow-up strategie heeft dan ook een grote (economische) impact. Er wordt veel energie gestoken in de ontwikkeling van diagnostische methoden om patiënten met een recidief van gedifferentieerd schildkliercarcinoom eerder te ontdekken. Echter, gedifferentieerd schildkliercarcinoom heeft over het algemeen een traag beloop en er is geen overtuigend bewijs dat eerdere ontdekking en behandeling van een recidief uiteindelijk invloed heeft op de mortaliteit (39). Dit is belangrijk om te realiseren omdat intensieve diagnostiek naar een recidief ook negatieve effecten kan hebben. Zoals beschreven in dit proefschrift, had het gebruik van een rhTSH gestimuleerde Tg meting een negatieve invloed op de kwaliteit van leven van een aanzienlijk aantal Tg positieve patiënten bij wie uiteindelijk geen recidief kon worden gelokaliseerd. Dit is ook een potentieel nadeel van de nieuwe ultrasensitieve Tg bepalingen. Het is mogelijk dat met deze bepalingen patiënten worden geïdentificeerd met minimale ziekteactiviteit die uiteindelijk nooit klinisch manifeste ziekte zullen ontwikkelen. Daarom is het essentieel de beschikbare diagnostische middelen op het juiste moment bij de juiste patiënt te gebruiken. Tijdens de follow-up van patiënten met een gedifferentieerd schildkliercarcinoom zou de nadruk niet

moeten liggen op het vaststellen van occulte ziekte bij patiënten, maar op het identificeren van die patiënten bij wie het gedifferentieerd schildkliercarcinoom zeer waarschijnlijk hun levensduur zal bekorten (40).

De introductie van ultrasensitieve Tg bepalingen is een belangrijke ontwikkeling in de follow-up van patiënten met gedifferentieerd schildkliercarcinoom. Zoals is beschreven in hoofdstuk 4, kan de introductie van een sensitieve chemiluminiscente immunoassay een eerdere ontdekking van een recidief tot gevolg hebben, die niet zou zijn gevonden met een conventionele Tg bepaling. De beperking van deze ultrasensitieve bepalingen is het aantonen van lage Tg concentraties bij een relatief grote groep patiënten bij wie geen recidief kan worden gelokaliseerd bij aanvullend onderzoek. Studies waarin patiënten met een net aantoonbaar Tg met een ultrasensitieve Tg bepaling langdurig worden vervolgd zijn nodig om de betekenis van deze lage Tg concentraties te kunnen vaststellen. Ook zullen nieuwe Tg afkapwaardes voor aanvullende diagnostiek moeten worden vastgesteld om daarmee overbodige diagnostiek te voorkomen. Een stijgende Tg concentratie is een veel sterkere aanwijzing voor een recidief, dan een (licht) verhoogde Tg concentratie die bij één enkele meting wordt vastgesteld. Het beloop van de Tg concentratie in de tijd dient dan ook een belangrijke rol te spelen bij klinische beslissingen. Alleen met deze voorwaarden kunnen ultrasensitieve Tg bepalingen bijdragen aan een optimale follow-up van patiënten met een gedifferentieerd schildkliercarcinoom.

Ondanks de introductie van het CRM-457 standaard preparaat (42,43) blijft er een aanzienlijke variatie bestaan in Tg waarden van verschillende Tg bepalingen tot wel een factor drie tot vier (44). Een verdere ontwikkeling van een harmonisatiemonster is nodig om deze interassay variabiliteit te beperken (44). Door de grote interassay variabiliteit is de bruikbaarheid van absolute Tg afkapwaardes die genoemd worden in richtlijnen voor de follow-up van gedifferentieerd schildkliercarcinoom beperkt en zal ieder instituut eigen Tg afkapwaardes moeten definiëren (44,46).

TgAb interferentie is een ander belangrijk methodologisch probleem bij de meting van Tg. Ook de nieuwe Tg bepalingen worden helaas gehinderd door TgAb interferentie waardoor Tg metingen onbetrouwbaar zijn indien TgAb aanwezig zijn. Het is onwaarschijnlijk dat in de nabije toekomst Tg bepalingen beschikbaar komen die geen interferentie van TgAb ondervinden. Daarom moet de aandacht vooral worden gericht op de ontwikkeling van methodes die accuraat TgAb interferentie kunnen detecteren. In de toekomst is mogelijk gelijktijdig gebruik van Tg recovery en kwantitatieve TgAb meting hiervoor de beste methode. Helaas is de in dit proefschrift onderzochte TgR bepaling niet meer beschikbaar en worden er weinig nieuwe TgR methodes ontwikkeld. Maar gezien de getoonde gunstige resultaten in dit proefschrift verdient de TgR bepaling hernieuwde aandacht. De ontwikkeling van accurate TgR bepalingen zal de follow-up van TgAb positieve patiënten vereenvoudigen. Daarnaast zal de waarde van TgAb concentraties als surrogaat maat voor ziekteactiviteit bij TgAb positieve patiënten verder onderzocht moeten worden. Een stijgende TgAb concentra-

tie zou kunnen wijzen op een toegenomen presentatie van schildkliertumor antigenen aan het immuunsysteem (11). Om deze hypothese te bevestigen zijn langdurige follow-up studies nodig waarin het gebruik van seriële TgAb metingen in patiënten met gedifferentieerd schildkliercarcinoom wordt geëvalueerd.

Gezien de complexiteit van de meting van Tg en TgAb interferentie is centralisatie van deze bepalingen in centra met de noodzakelijke expertise aan te bevelen. Een centralisatie maakt het eveneens mogelijk om Tg afkapwaardes vast te stellen voor alle patiënten met gedifferentieerd schildkliercarcinoom die vervolgd worden in de geaffilieerde ziekenhuizen.

RhTSH is geïntroduceerd als praktisch hulpmiddel in de follow-up om TSH stimulatie te bereiken zonder het onttrekken van schildklierhormoon, voor Tg metingen en diagnostische radioactief jodiumscans. Echter, zoals aangetoond in dit proefschrift en ook in andere studies (28-30), is de rhTSH gestimuleerde Tg meting in de lange termijn follow-up niet bijdragend. Daarnaast is de sensitiviteit van de diagnostische jodiumscans laag en worden deze tegenwoordig steeds minder gebruikt tijdens de follow-up (47,48). Dit betekent dan ook dat de waarde van rhTSH voor de Tg bepaling en diagnostische jodiumscan in de lange termijn follow-up beperkt is. Echter, veelbelovende toepassingen van rhTSH zijn het gebruik bij de FDG-PET scan en de ablatietherapie met radioactief jodium. Omdat rhTSH in vergelijking met het onttrekken van schildklierhormoon gunstig is voor de kwaliteit van leven van schildkliercarcinoompatiënten, verdienen deze potentiële toepassingen een zorgvuldige beoordeling.

De follow-up van laag-risico schildkliercarcinoompatiënten (70-85% van de gehele groep schildkliercarcinoompatiënten) is goed gedefinieerd. Algemeen wordt aangenomen dat hoog-risico patiënten intensiever vervolgd moeten worden, maar een wetenschappelijk onderbouwd follow-up protocol voor deze patiëntengroep ontbreekt. Bovendien voorspellen de huidige risicostratificatiesystemen niet altijd juist de uiteindelijke uitkomst. Het herstadiëren van patiënten op basis van de respons op initiële therapie zou kunnen bijdragen aan een betere voorspelling van de kans op een recidief en overlijden (34). Daarnaast kan het karakteriseren van schildkliertumoren met nieuwe moleculaire technieken een belangrijke bijdrage leveren aan risicostratificatie. In de laatste decennia is er een enorme vooruitgang geboekt in de kennis op het gebied van moleculaire veranderingen betrokken bij het ontstaan van gedifferentieerd schildkliercarcinoom. Het vaststellen van moleculaire eigenschappen van agressieve en niet-agressieve gedifferentieerde schildkliercarcinomen zal in de toekomst dan ook gebruikt kunnen worden voor een meer accurate risicostratificatie. Daarmee kan het follow-up protocol aangepast worden op de individuele patiënt met betrekking tot het risico op een recidief.

Een kleine groep patiënten heeft een progressief gedifferentieerd schildkliercarcinoom dat tot de dood leidt. Lokale behandelmogelijkheden, zoals embolisatie van botmetastasen, zijn van belang voor het verminderen van klachten. Helaas zijn systemische behandelmogelijkheden voor patiënten met een gemetastaseerd schildkliercarcinoom dat geen ra-

dioactief jodium opneemt beperkt. De resultaten van chemotherapie zijn op dit moment teleurstellend. Recente ontwikkelingen in de moleculaire oncologie hebben echter geleid tot de ontwikkeling van veelbelovende middelen gericht op groeifactoren, intracellulaire receptor kinasen en "downstream" mediatoren van celsignalering. Enkele van deze nieuwe middelen, bijvoorbeeld Axitinib en Sorafenib, allebei tyrosine kinase remmers, hebben in fase II onderzoeken klinisch relevante antitumor activiteit bij patiënten met gemetastaseerd schildkliercarcinoom (49,50).

Concluderend is de follow-up en behandeling van gedifferentieerd schildkliercarcinoom sterk in ontwikkeling. De sterk verbeterde sensitiviteit van de diagnostiek in de follow-up van patiënten met een gedifferentieerd schildkliercarcinoom maakt het noodzakelijk om die groep patiënten te identificeren voor wie de toepassing van deze diagnostiek daadwerkelijk klinisch belang heeft, om zo de belasting voor patiënten en de kosten te beperken. Er wordt uitgezien naar nieuwe ontwikkelingen op het gebied van de moleculaire biologie die een bijdrage kunnen leveren aan zowel de risicostratificatie als nieuwe behandelmogelijkheden.

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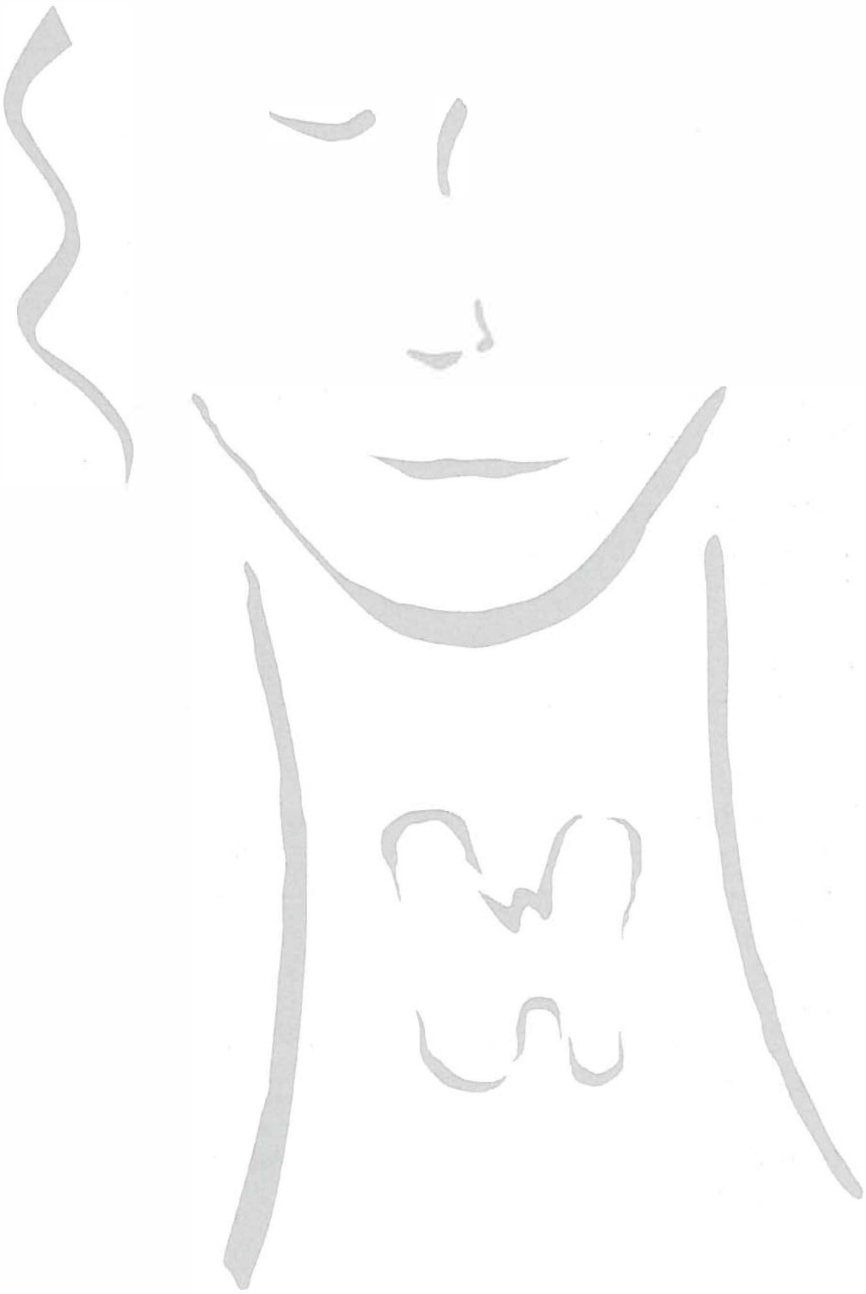

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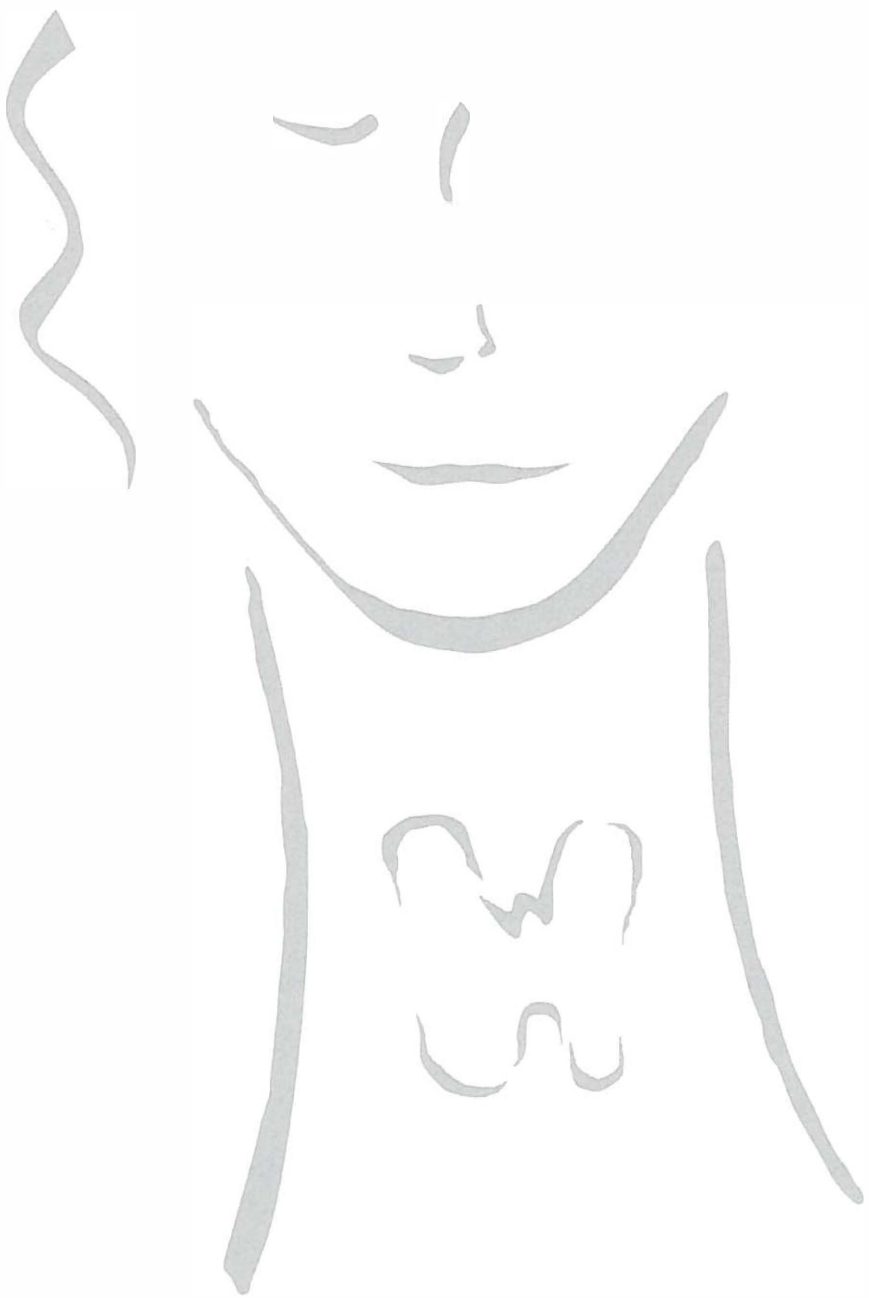
Woord van dank



**De wetenschappen beoefenen en de mensen niet liefhebben,
is hetzelfde als een fakkel ontsteken en de ogen sluiten.**

Chinese wijsheid

WOORD VAN DANK

Deze laatste regels in dit proefschrift weerspiegelen mijn dankbaarheid aan hen die gaven wat nodig was. Ik prijs me gelukkig dat ik omringd ben door mensen met een grote passie en liefde voor hun vak. Niets is zo inspirerend en motiverend als dat.

Dr. T.P. Links, copromotor en belangrijkste grondlegger van dit proefschrift. Lieve Thera, ooit koos ik achteloos je naam uit het ziekenhuistelefoonboek omdat ik een begeleider zocht voor mijn wetenschappelijke stage in Zuid-Afrika. Deze stap is achteraf gezien alles bepalend geweest voor mijn verdere toekomst tot nu toe. Jij bent steeds mijn grote inspirator geweest, als wetenschapper, als dokter en als mens. Jij was altijd dichtbij. Ik ben blij en trots dat je deelgenoot bent van het eindresultaat.

Mijn promotoren, Prof. dr. B.H.R. Wolffenbuttel en Prof. dr. P.L. Jager.

Beste Bruce, je hebt mij het vertrouwen gegeven dit proefschrift te kunnen voltooien. Op de beslissende momenten waren je oog voor de kern van de zaak en heldere formuleringen vaak van doorslaggevende aard. Veel dank daarvoor. Ik heb grote bewondering voor je visie en daadkracht waarmee je grootse zaken tot stand weet te brengen.

Beste Piet, wat een eer om ook jou als promotor te hebben. Kenmerkend is jouw positief-kritische houding waarmee je een grote bijdrage aan dit proefschrift hebt geleverd. Dank dat je me altijd het gevoel hebt gegeven dat het goed kwam.

Mijn andere onmisbare copromotor, Dr. W.J. Sluiter. Beste Wim, bij methodologische of statistische obstakels deed een bezoek aan jou altijd weer wonderen. Dank voor deze ondersteuning maar meer nog voor je nuchtere en verhelderende kijk op de wetenschap en het leven.

Dr. J.M.W. van den Ouweland. Beste Jody, je bent de motor geweest achter twee belangrijke artikelen in dit proefschrift. Veel dank dat je als toegewijde en deskundige klinisch chemicus een onmisbare schakel in dit proefschrift hebt willen zijn. "De aanhouder wint" was een terugkerend motto binnen onze samenwerking en heeft uiteindelijk tot mooie resultaten geleid. Samenwerken met jou was een genot.

De medewerking van zeer veel mensen is essentieel geweest voor het slagen van de "rhTSH-studie". Grote dank gaat allereerst uit naar alle patiënten die hebben deelgenomen aan deze studie. Zonder hen was dit proefschrift nooit tot stand gekomen.

Voor een goede organisatie van de studie en registratie van studieresultaten kreeg ik voortreffelijke steun van Baukje Fokkens en Inge Pop. Met grote zorgvuldigheid hebben jullie monnikenwerk verricht, tevens brachten jullie veel gezelligheid in de Triadekamer. Dank je wel! Ook het secretariaat en de poli endocrinologie wil ik bedanken voor hun ondersteuning bij de studies en al die andere soms kleine dingen die een groot verschil maken.

Rita van Slooten heeft tevens met grote zorg en toewijding gewerkt aan de onderzoeksregistratie, helaas hebben wij veel te vroeg afscheid van haar moeten nemen.

De afdeling Nucleaire geneeskunde, waarbij ik Ha Phan en Adrienne Brouwers in het bijzonder wil noemen, dank ik voor hun grote inzet voor de nucleaire beeldvorming en de zeer plezierige samenwerking. Ook dank aan het PET-centrum, de afdeling Radiologie (echografie) en Joost Gravendeel voor hun bijdrage aan het slagen van de beeldvormende diagnostiek in deze studie. John Plukker bedank ik voor zijn bijdrage vanuit de chirurgie.

Zorg voor de kwaliteit van leven van patiënten houdt mij dagelijks bezig, maar een kwaliteit van leven-studie uitvoeren is niet altijd eenvoudig voor een medicus. Prof. dr. A.V. Ranchor (Noordelijk Centrum voor Gezondheidsvraagstukken) en dr. Keers, beste Adelita en Joost, dank voor het geven van jullie waardevolle visie vanuit de psychologie op de resultaten van deze studie.

Veel dank ben ik ook verschuldigd aan dr. H. Groen (Afdeling Epidemiologie) voor zijn hulp bij het opzetten van de kosteneffectiviteitsanalyse en dr. K.M. Vermeulen (Afdeling Epidemiologie). Beste Karin, je hebt me elke keer weer verbaasd hoe verbluffend snel je onze studieresultaten doorzag. Dank voor de zeer prettige samenwerking.

Alle stafleden van de afdeling Endocrinologie wil ik hartelijk bedanken voor hun interesse, hulp en de goede werksfeer.

Margriet de Vries, jouw enthousiasme en doorzettingsvermogen hebben geleid tot een mooi artikel. Dank daarvoor. Juergen Wilde, Eduard Heine en Jan Koerts wil ik bedanken voor hun (praktische) bijdrage aan de evaluatie van de thyreoglobuline assay.

De leden van de beoordelingscommissie Prof. dr. I.P. Kema, Prof. dr. J.W.A. Smit en Prof. dr. E.G.E. de Vries wil ik hartelijk bedanken voor hun bereidheid dit proefschrift te beoordelen.

Op de Triadekamer heb ik vele vermakelijke uren doorgebracht met Helen Lutgers, Martine v.d. Hem, Rindert de Vries, Susan Borggreve en Udo Mulder. Dank je wel voor deze fantastische tijd samen. Susan, Rindert en Udo waren de mede-onderzoekers van het eerste uur.

Susan, jouw eigenheid is je grote kracht en maakte onze tijd samen op de Triadekamer tot een kleurrijke periode.

Rindert, ik vind het een eer om aan je zijde te mogen staan als paranimf. Het is een kroon op een goede vriendschap.

Udo, na onze onderzoekstijd ben ik je in het Martini ziekenhuis alleen nog maar meer gaan waarderen. Als poli-maatjes liepen we de deur bij elkaar plat voor goede raad, een mooi verhaal over een 'spot-diagnose', en koffie. Laten we dat nog lang blijven doen.

Tegelijkertijd met het schrijven van deze laatste woorden in dit proefschrift, komt ook een einde aan mijn opleiding in het Martini ziekenhuis. Ik sluit een mooie tijd af, waarin een stevig fundament is gelegd voor de toekomst. Alle internisten (opleider dr. W.M.T. Janssen, voormalig opleider dr. R.S. de Jong) wil ik bedanken voor hun persoonlijke inzet voor een goed opleidingsklimaat. Op deze plaats wil ik ook dr. K.M. van Tol bedanken. Beste Karin, ik heb dankbaar gebruik gemaakt van het door jou verzamelde cohort schildklier-carcinoompatiënten. Fijn dat ik ook in het Martini ziekenhuis veel van je heb mogen leren. Tevens wil ik de collega-assistenten, intensivisten, cardiologen, longartsen en maag-darm-leverartsen bedanken voor de prettige en leerzame tijd. Een nieuwe uitdaging in het UMCG ligt voor me (opleider Prof. dr. R.O.B. Gans).

Mijn paranimfen Suzanne Klene en Liesbeth Simmelink, wij zijn vriendinnen sinds onze eerste uurtjes in de collegebanken.

Lieve Suus, met jou heb ik heel wat (Afrikaanse) stormen doorstaan, dus dit kunnen we ook wel aan. "Happiness' is ons toverwoord, ik hoop dat we samen nog heel veel happiness mogen beleven.

Lieve Liesbeth, ik word altijd weer blij van jouw enthousiasme, oprechte interesse en trouw. Dat is me heel dierbaar. Die St. Pietersberg gaan we met zijn drieën halen, ook al zullen we met ons huidige tempo dan waarschijnlijk omaatjes van 80 jaar zijn!

Mijn vrienden en vriendinnen, dank voor alles wat we samen delen en het leven zo mooi maakt.

Altijd kan ik rekenen op de onvoorwaardelijke steun van familie. Mijn lieve schoonfamilie: ik heb het met jullie getroffen! Lieve Middendorpjes, van kleins af aan doen we alles samen, eigenlijk heb ik 4 broers en twee zusjes. Fijn dat we bij elkaar horen.
Lieve pap, mam, Gerald, Laurens en Bettie, jullie zijn de bron van alles waar ik nu voor sta. Dank je wel dat thuiskomen altijd weer zo goed is.

Lieve Bastiaan, ik geloof in jou en mij.